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MELANOMA STUDIES *

III. A THEORY OF PIGMENTED MOLES. THEIR RELATION TO THE EVOLUTION OF HAIR FOLLICLES

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I. THE PIGMENTED MOLE AS A TACTILE TUMOR

Discussion of the origin of pigmented moles should begin with a mutual understanding of just what a pigmented mole is. All readers will agree, we believe, that the pigmented mole is an abnormal growth in human skin, that it is pigmented, usually elevated, often hairy, and that on microscopic examination groups of nevus cells are found in the corium. We shall make the further claim that the pigmented mole shows distinct traces of having been at one time a tactile organ with a full complement of sensory nerves and tactile terminals. It is at this point that differences of opinion arise. It is at this point therefore that we shall begin to present our evidence.

Nerve Terminals in Moles

Any good neural silver stain applied to a pigmented mole will reveal branching nerve trunks, as pictured in Figure 1. There is

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nothing unusual about a nerve trunk branching in human skin. All normal skin offers these pictures. We would direct attention to the smaller branch which leaves the crotch of the main trunk and passes to the right. This nerve divides and subdivides into fine threads. The threads terminate in tiny bulbs in contact with some of the nevus cells which form the background of the picture. This is exactly the manner in which many nerves terminate among the Merkel-Ranvier tactile cells of the hair follicles and the basal cells of the epidermis. Such a distribution of nerve fibers is never found in normal human corium but it is a common sight in pigmented moles.

Figure 2 shows a more elaborate distribution of nerves in another mole. The background is a solid sheet of nevus cells among which the nerve fibers ramify, the fine threads winding around the nevus cells and terminating as tiny end-bulbs in intimate contact with some of them.

Figure 3 shows another neural distribution which is common in hairy moles. The most prominent feature of the picture is the hair in its follicle. At the left of the follicle a nerve divides. Some of the branches pass upward and to the right to supply the follicle. These nerves terminate in tiny end-bulbs in contact with epithelial cells of the follicle, which consequently are regarded as cells specialized for the reception of tactile impulses. Other branches diverge upward to the left and downward to the right. These branches terminate in end-bulbs on and among the nevus cells. If the epithelia of the hair follicle are accepted as specialized tactile cells by virtue of their innervation it is a fair proposition that the nevus cells also are tactile cells by virtue of an exactly similar innervation. Pictures of such joint innervation of hair follicles and nevus cells might be multiplied indefinitely.

The tactile nature of these neval nerves was demonstrated in another way by Masson (1926, 1931, 1932),[1, 2, 3] as shown in Figure 4, a Masson-Mallory trichrome stain of a paraffin section of a mole from the occiput. The section is from Professor Stout's collection. Like many moles on or near the scalp, this one is crowded with figures which Masson first described and, we believe, interpreted rightly as caricatures of meissnerian tactile corpuscles. Masson's demonstration of tactile corpuscles in pigmented moles has been corroborated by Stout (1932),[4] Ewing (1928, 1930),[5, 6] Foot (1931),[7] who

presented convincing preparations at the meeting of the American Association of Pathologists and Bacteriologists in Philadelphia last year, and by Frantz and McFarland (personal communications).

Figure 5 shows another common sight in pigmented moles when stained for nerve fibers. It is what we call the cable effect. Around a few neurites traversing the colorless corium there is an enormously thick sheath of cells. Such pictures are characteristic of von Recklinghausen's neurofibroma of the skin; in fact, it was this formation that led Soldán (1899)[8] to declare unequivocally that the pigmented mole is a neurofibroma. Using Weigert's myelin stain Soldán demonstrated medullated fibers only; he did not use silver.

Figure 6 is a normal meissnerian corpuscle from the sole of the human foot. It is introduced for two purposes, to show that our staining technique is actually specific for nerve fibers and to demonstrate that, with this technique at least, the nerves are seen to terminate among the well recognized tactile cells of the meissnerian corpuscle exactly as they do among the nevus cells.

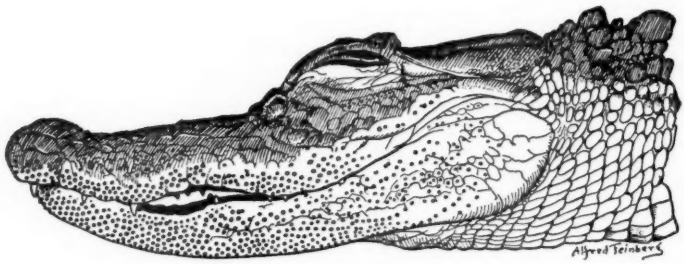
Assuming that we have come to an agreement that pigmented moles contain sensory nerve fibers and cells that appear to be tactile cells because of their neural contacts, together with structures resembling meissnerian tactile corpuscles, let us pass to a consideration of their possible origin. For all tumors or for almost all tumors, there is a prototype, that is, some adult or embryonic tissue of which the tumor is a more or less faithful reproduction. It is a striking feature of pigmented moles that they do not resemble anything known in normal mammalian skin. No normal mammalian corium contains groups of cells, innervated, pigmented and elevated in the manner characteristic of pigmented moles. If, however, we look at the creatures just below the mammals in the phylogenetic scale, the reptiles and the amphibia, we shall find them peppered with pigmented dots which on microscopic examination present the structure of human pigmented moles.

II. The Reptilian Tactile Spot

Text-figure 1 represents the head of the common alligator. Along the upper and lower jaws there are many black dots standing out prominently on the smooth, white skin. Each dot is a sensory nerve terminal, generally accepted by zoölogists as a tactile organ. Such tactile organs are common to reptiles and amphibia. They were dis-

covered in the frog by Merkel (1880)[9] and called by him *Tastflecke*, tactile spots.

Figure 7 is a vertical section through one of these tactile spots stained for nerve fibers. You will note that the tactile spot is elevated and pigmented, and that there is a group of cells in the corium just beneath the epidermis. These are Merkel-Ranvier tactile cells mixed with Schwann cells from the nerve fibers. The ascending nerve breaks into fine terminal threads which wander among the tactile cells just as similar terminal threads wander among the nevus cells. Some of the threads terminate as end-bulbs, some as menisci, in contact with a tactile cell; some continue on into the epidermis. You will recognize the resemblance of this structure to that of the



TEXT-FIG. 1. Alligator Missisippiensis

innervated pigmented mole. There is the same elevation, the local accumulation of pigment, the group of tactile cells in the corium and the fine nerve fibers winding among the tactile cells, terminating on some of them as end-bulbs and menisci.

Figure 8 is a tactile spot from the palate of the alligator. There is no pigment to confuse the picture and you may have a clearer view of the group of tactile cells in the corium, separated from the epidermis by a narrow strip of corium, and the nerve fibers terminating on and among the tactile cells.

Good illustrations of the microscopic appearance of tactile spots may be seen in the reports of Merkel (1880)[9] and Hulanicka (1909, 1913).[10, 11] Pinkus (1927, p. 346)[12] reproduces one of Hulanicka's drawings of a tactile spot of the alligator's tongue, which bears a striking resemblance to the microscopic picture of a pigmented mole.

The question now arises — What possible connection can there

be between pigmented moles of human skin and these pigmented reptilian spots that resemble them so closely? The answer is to be found in the evolution of the hair follicle.

III. The Evolution of the Mammalian Hair Follicle

In the course of evolution, as the mammal evolved from a reptilian form, the reptilian tactile spots disappeared. As tactile organs they were replaced by hair follicles, which appeared first in mammalian skin.* If we can picture to ourselves a point on mammalian skin where this transformation has not taken place completely, a point where hair follicles have appeared but where reptilian tactile spots have not disappeared, we should have a fair picture of a pigmented, hairy mole. Insert a few hairs in the tactile spots of this alligator and again you would have a good likeness of a hairy, pigmented mole.

The pigmented, hairy mole, then, appears to be a link or transition from pigmented tactile organs of the amphibian-reptilian type to hairy tactile organs of the mammalian type. It offers a picture that is only partly mammalian, the other part being reptilian. In its hair follicles it is mammalian; in its pigmentation, elevation and in the groups of innervated tactile cells in the corium it follows the amphibian-reptilian pattern.

We are well aware of the obscurity that veils the early steps of the evolution of mammalian hair. Animals intermediate between reptile and mammal have largely disappeared or are known only as fossils, of little use in the study of nerve terminals. We are familiar also with the hypotheses by which Maurer (1892, 1895, 1922),[15, 16, 17] Oppenheimer (1896),[18] Botezat (1914),[14] Broman (1920, 1921),[19, 20] Preiss (1922),[21] Plate (1922)[22] and others have sought to bridge this evolutionary gap. Discussions and bibliographies may be found in Botezat (1914),[14] Pinkus (1927)[12] and de Meijere (1931).[23] Among these varied and often conflicting opinions the chief supports of our hypothesis stand unshaken. Everyone agrees that the skin of modern reptiles and amphibia contains innumerable tactile spots and that in some manner mammalian skin has succeeded in replacing the reptilian tactile spots with mammalian hair.

* Zoölogists hold that hair is primarily a tactile organ, adapted secondarily to the functions of color and bodily warmth (Plate, 1922, p. 308,[13] Botezat, 1914, p. 25, 27, 31[14]).

Der Spitzmaus

The possibility of the persistence in mammalian skin of nerve terminals resembling amphibian tactile spots needs no lengthy argument, for it actually occurs in one of the shrews. Merkel himself, discoverer of the tactile spot, writes that among the hair follicles on the back of the Spitzmaus (*Sorex pygmaeus*) he saw "nerve fibers ending in groups of cells which lay just beneath the epidermis. These are certainly end-organs but they looked much more like amphibian tactile spots than the customary tactile corpuscles of mammals" (1880, p. 143).[9]

IV. The Pigmented Mole as a Phylogenetic Tumor

The more imaginative of the medical profession have long held a vague belief in the existence of phylogenetic tumors (Bland-Sutton, 1893, p. 493),[24] and among phylogenetic tumors they have been especially impressed by the resemblance of hairy moles to the skin of the lower mammals. Pathologists generally had accepted Cohnheim's teaching (1877)[25] of the origin of certain tumors in groups of cells that had remained unutilized in the building of the human embryo, when Ribbert (1906)[26] pushed some origins farther back and declared that uterine adenomyoma, intestinal polyposis and pigmented moles could not be explained as aberrations in the growth of the human embryo, but that they were easily intelligible as imperfect survivals of structures normal to animals lower in the phylogenetic scale. Mathias (1920, 1922)[27, 28] came to the same conclusion concerning tumors arising in aberrant pancreas and parotid tissue, noting that such scattered distribution of these glands is normal in earlier evolutionary forms. He proposed grouping such tumors under the name progonoblastoma (*progonoi*, ancestors), and Jendralski (1921)[29] described a pigmented mole of the conjunctiva as a progonoblastoma.*

Meirowsky (1926)[30] wrote of congenital vitiligo and pigmentation: "Since they correspond so closely with the markings of the lower animals, it follows that in human skin there exist phylogenetically fixed localizations in which a change to nevus formation can occur."

* Mathias (1922)[28] announced a forthcoming publication to be entitled: "Zur Auffassung der Naevi als Atavismen im Sinne der Progonoblastom." This paper was never published (personal letter).

Searching in human skin for some vestige of the tactile hairs (sinus hairs) which are widespread among mammals other than man, Henneberg (1915)[31] thought to find them in pigmented, hairy moles, a view advanced also by Friedenthal (1908),[32] by Sklarz (1926),[33] and by Sulc (1926),[34] who includes vascular nevi as vestiges of the blood sinuses of sinus hairs. In this group of phylogenetic tumors, Šikl (1932)[35] inclines to place two benign epitheliomas of human skin containing mucus-secreting goblet cells, a common feature of the skin of the lower vertebrates but known among mammals only in the skin of the hippopotamus; and Kyrle (1925, p. 253)[36] regards human syringocystadenoma as a vestige of the apocrine glands of the lower mammals.

The ideas of this period were well summarized by Maurer (1929)[37]: "A man is not merely the child of his parents. He is rather the end-product of an immeasurable line of ancestors whose witnesses are the single steps of his embryonic evolution and the many vestiges in his finished form. Such testimony shows that the genes of the impregnated ovum contain the hereditary factors of many different types of animals." *

Back to the Reptile

In explaining the origin of pigmented moles on the principle of phylogenetic atavism all writers without exception have made the same blunder. They forget the nevus cells. From Ribbert onward, they have compared moles in a general way to "the pigmented skin of the lower animals," or more specifically to the hairy tubercles of mammals other than man. But there are no nevus cells in the pigmented skin of the lower mammals or even in their hairy tubercles, whereas nevus cells are an almost constant feature of pigmented moles. Moreover these writers overlooked the nerve fibers. Since the work of Soldán, and especially of Masson, we can no longer hold the simple view that pigmented moles are mere bits of brown or hairy skin inherited from remote mammalian ancestors. When Masson showed that pigmented moles are tumors of the sensory nerves of the skin, that some of the nerves terminate on the nevus

* The phylogenetic sequence of pigmented, hairy moles may be viewed in reverse, making the mole itself the starting point of anthropological studies and working backward, as Samberger (1933)[38] has done with naevus acanthosiformis.

cells, and that some pigmented moles contain myriads of meissnerian tactile corpuscles, he obliged the palingeneticist to shift his ground from the study of remote ancestors with pigmented, hairy skins to the study of remote ancestors with pigmented tactile terminals buried in the corium. In so doing we must pass over the entire series of mammals, where no such terminals exist (the end-organs of Merkel's shrew are neither pigmented nor elevated), to ancestors still more remote, the reptiles and amphibia, where pigmented tactile terminals buried in the corium abound. Here at last in the reptilian tactile spot we find a full length portrait of the human pigmented mole, a pigmented elevation of the skin and a nerve coming up from below to innervate a group of tactile cells in the corium.

A phylogenetic theory of pigmented moles must give nerve fibers and nevus cells equal rank with hair and pigmentation. It is true that hair, pigmentation and nerve fibers might represent merely the reappearance in human skin of a patch of mammalian hair, but the innervated nevus cells inexorably carry us farther back, linking that mammalian hair with its evolutionary predecessor, the reptilian tactile spot.

V. Ontogenesis

Whether or not we accept a phylogenetic influence in the formation of the pigmented, hairy mole in human skin, we must still seek the immediate fault in the skin of the individual possessing the mole, in ontogenesis. In this search the reptilian aspect of the pigmented mole may prove to be a useful guide. Since the mole is overwhelmingly congenital and often hereditary its ground must have been laid during embryonic life. There is then a certain point in the growth of human embryonic skin when the dipping epidermis and the advancing nerve fibers, which normally coöperate to construct innervated hair follicles, revert to the construction of innervated reptilian tactile organs. One would be inclined to seek this point in a stage of the human embryo when it has not yet diverged greatly from the form and potencies of the reptilian embryo.

Experimental embryology is showing that the various tissues, and in some cases organs, which develop harmoniously to form the individual, are determined very early in embryonic life (Lillie, 1929).[39] That is to say, an irreversible change occurs in the nature of the still undifferentiated part which restricts its future capacity for de-

velopment. By such a restrictive change, for example, the cells composing the primitive ectoderm are segregated into those capable of developing into neural tissue and those whose potency is restricted to the production of epidermis. Parts of the epidermis in their turn are progressively restricted to the production of lens, and so on, and finally hair, feathers and other late appearing structures. There are relatively few kinds of such segregates, and the number varies but little throughout the whole vertebrate series.

In the ontogenetic development of the mammal, as compared with that of the reptile, hair appears as a new segregate and simultaneously the tactile spot is lost. If these two organs could be conceived of as segregates from a predecessor equipotential for both, hair being induced by conditions normal to the developing mammalian skin and the tactile spot by conditions normal to the developing reptile, the appearance of the congenital pigmented mole in mammalian skin might be postulated as due to some slight local variation in environment at a critical period. Such a local variation might be of circulatory or neural origin.

The Vascular Nevus

The phylogenetic hypothesis might be extended to vascular nevi. The most primitive amphibia had no lungs; they breathed entirely through the skin. Many salamanders living today have preserved this primitive type of respiration, bearing in their skins a rich capillary plexus that serves as a cutaneous lung. The capillary plexus of vascular nevi may be interpreted as a vestige of the respiratory plexus inherited from that far-off ancestor, the primitive amphibian that breathed through the skin.

Summary

Photomicrographs of silver-stained sections are presented to show that pigmented moles are rich in nerve fibers and tactile cells. Endbulbs of nerve fibers make contact with nevus cells exactly as they do with the tactile cells of the epidermis and of the hair follicles.

Masson's observation of a profusion of structures resembling meissnerian tactile corpuscles in certain pigmented moles is confirmed.

In its elevation, pigmentation, innervation and the groups of tactile cells in the corium, the pigmented mole bears a striking resemblance to the tactile spots of reptiles and amphibia.

In the course of evolution the reptilian tactile spots were replaced by mammalian hair follicles. The pigmented, hairy mole appears to be a link or transition from pigmented tactile organs of the reptilian type to hairy tactile organs of the mammalian type. In its hair follicles it is mammalian, in its pigmentation, elevation and in the groups of innervated tactile cells in the corium it follows the amphibian-reptilian pattern.

Phylogenetic and ontogenetic hypotheses are presented.

For helpful criticism and advice on zoölogical questions and for reptilian material we are indebted to Dr. G. Kingsley Noble of the American Museum of Natural History, to Drs. H. E. Anthony and George G. Goodwin of the same Museum, and to Dr. W. J. Hamilton, Jr., of Cornell University for specimens of American shrews. Dr. Jerome Webster has long taken a friendly interest in these studies, contributing many pigmented moles from his clinic of plastic surgery. To Professor Purdy Stout, the most generous and self-effacing of laboratory directors, we owe many valuable suggestions and choice material.

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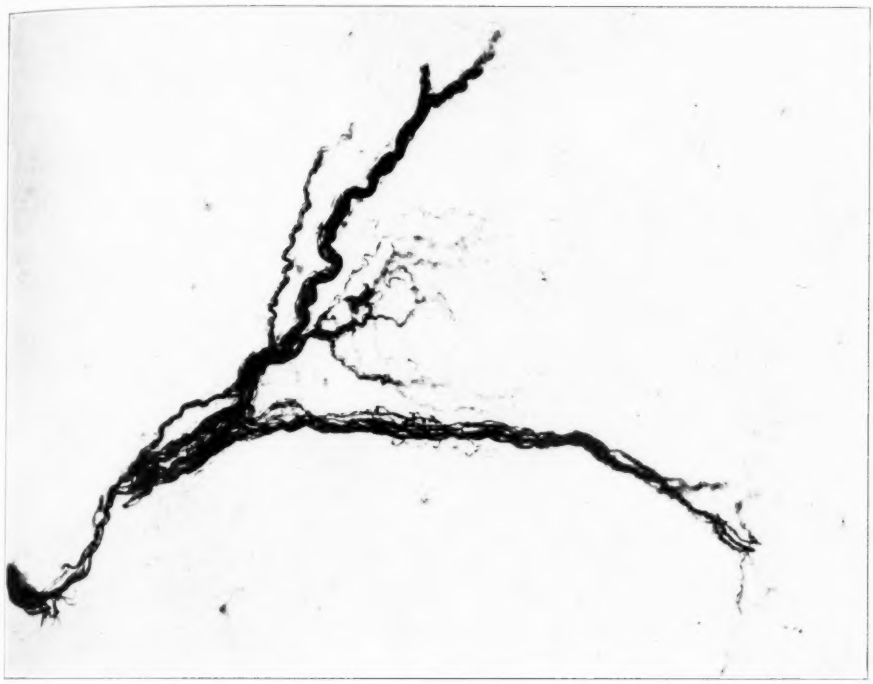
DESCRIPTION OF PLATES

With the exception of the paraffin section of Figure 4, all tissue was fixed in formalin slightly alkalinized with sodium hydrate or pyridin. Thick frozen sections were stained by Laidlaw's 2 minute silver technique for neurites. This is a modification of Gros-Bielschowsky. Gold toning was omitted. With this technique collagen is usually colorless, cytoplasm colorless to pale yellow, nuclei yellow to brown, and neurites black. The sections are cut very thick, 50 to 75 microns, in order to follow the course of the nerves for long distances. With these black neurites on a colorless or pale yellow ground thickness of the section is no obstacle to satisfactory microscopic examination, although thick sections are not so suitable for photography. Photomicrographs were taken through Wratten filters.

PLATE 133

FIG 1. A nerve trunk branching in the center of a very cellular pigmented mole. The ground is a broad sheet of nevus cells, pale yellow in the section but scarcely distinguishable in the photograph. Just above the crotch of the nerve a short branch goes to the right, soon breaking into fine threads that wind among the nevus cells and end on some of them as tiny bulbs. This is the characteristic termination on tactile cells.

FIG. 2. Distribution of a nerve in a pigmented mole. The entire background is a broad sheet of nevus cells, seen indistinctly in the picture. At the left a nerve trunk gives off many delicate threads that wander among the nevus cells and end as tiny bulbs on some of them. The black figures on the extreme right are short sections of nerve trunks.



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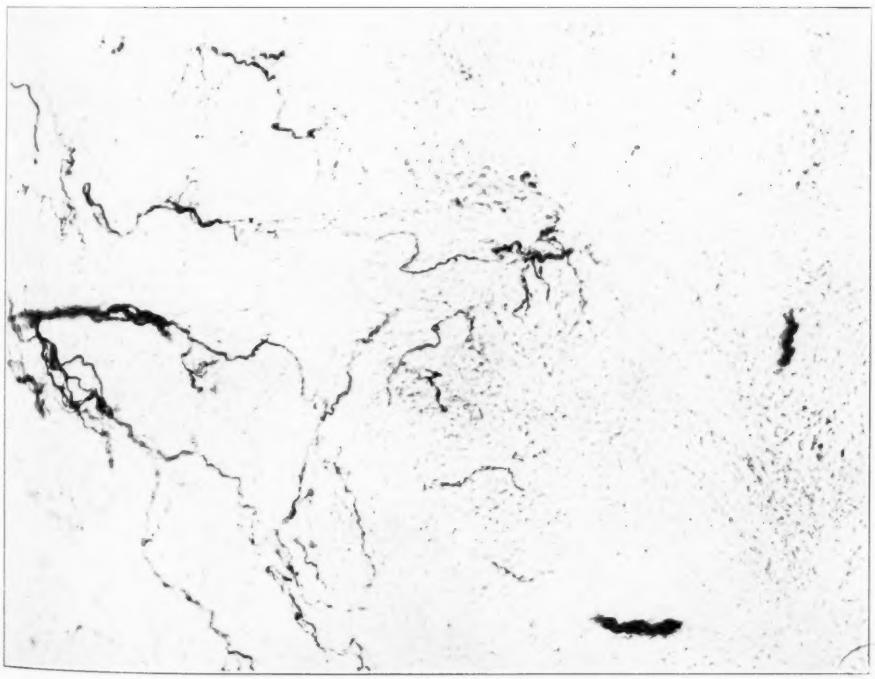

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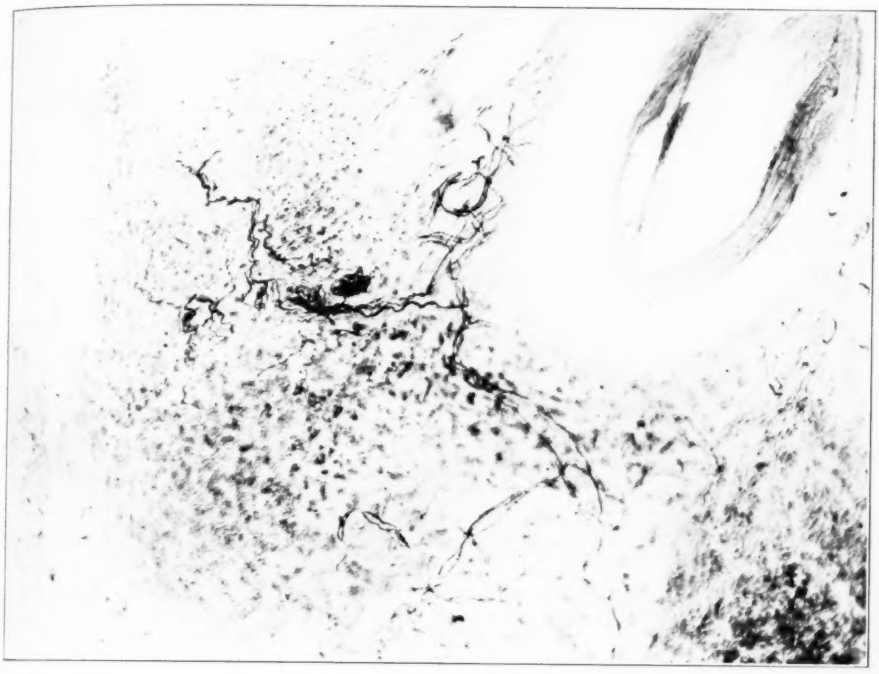
PLATE 134

FIG. 3. Joint distribution of a nerve to a hair follicle and to the surrounding nevus cells. In the right upper corner is a hair in its follicle. The epithelium of the sheath is invisible, colorless in the section. The rest of the picture is a broad sheet of nevus cells. In the center a cross-section of a nerve trunk is seen just at the point where it is dividing. Some branches pass upward and to the right to supply the sheath of the hair follicle. These branches end as tiny bulbs among the epithelia of the hair follicle. Other branches pass upward to the left and downward to the right among the nevus cells. These branches end as tiny bulbs on the nevus cells exactly as the other branches end on the tactile epithelia of the hair follicle. Such joint innervation of hair follicles and nevus cells is very frequent.

FIG. 4. Paraffin section of a pigmented mole from the occiput, fixed in Bouin's fluid. Masson-Mallory trichrome stain. Instead of the usual groups of nevus cells this mole consists almost entirely of round and oval figures, laminated and nucleated, closely resembling meissnerian tactile corpuscles.



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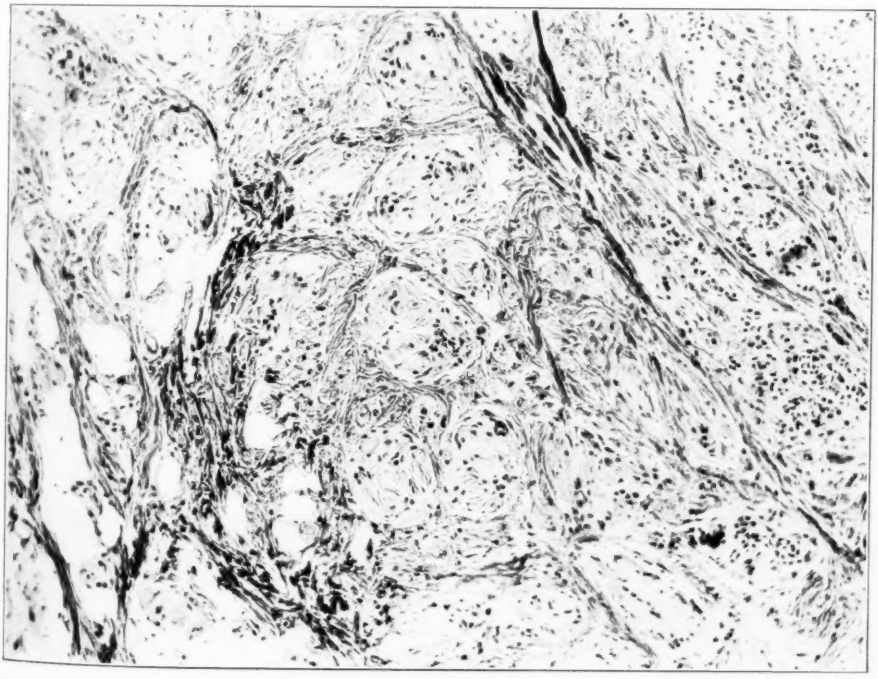

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Laidlaw and Murray Melanoma Studies. III

PLATE 135

FIG. 5. From the margin of a pigmented mole. The dark band across the top is epidermis, moderately pigmented but unduly blackened by the silver. Well below the epidermis, running across the colorless corium, is a slender bundle of black neurites, cut by the knife into three sections. The neurites are enclosed in a very thick sheath of cells that blend with the surrounding corium without sharp demarcation. There is no limiting perineurium. This formation is characteristic of neurofibroma of the skin.

FIG. 6. Nerve skein of normal meissnerian corpuscle from the sole of a human foot. The corpuscle lies in a broad, colorless papilla. The irregular black band above it and to the left is normal epidermis. Of the nuclei of the corpuscle, only a few are stained. The nerve skein of the corpuscle is broken into three sections, as often seen in these long corpuscles. The neurites end as bulbs of various sizes in contact with the tactile cells of the corpuscle. In some corpuscles the end-bulbs are enormous. Just below these corpuscles lateral branches often leave the nerve to supply the adjoining epidermis.

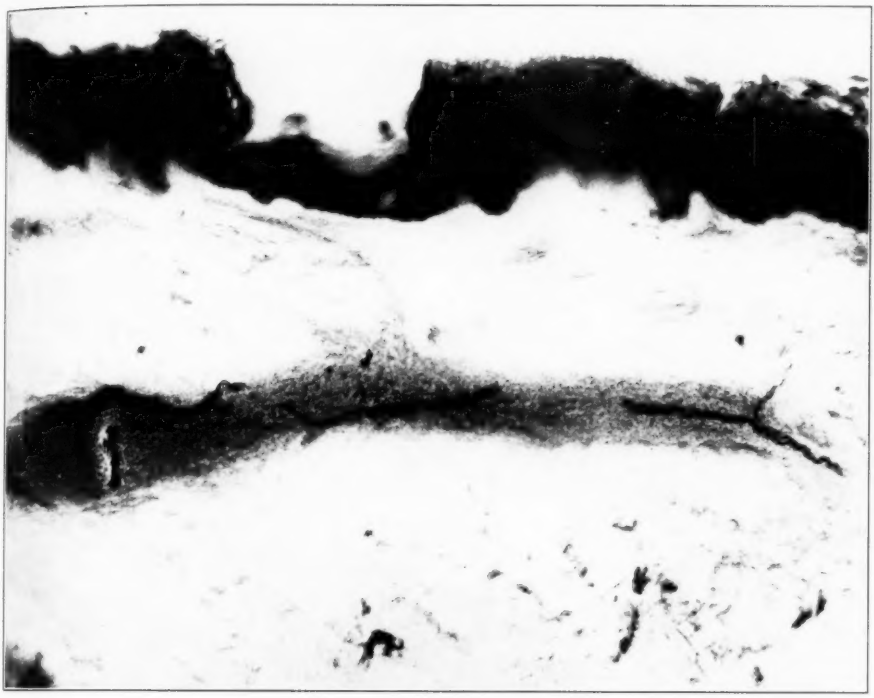

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PLATE 136

FIG. 7. Vertical section through the black tactile spot of an alligator's jaw. Note the conical elevation of the derma with its group of tactile cells. In the natural state the pigmentation is limited to the elevation; in the picture the whole epidermis has blackened in the silver. The black figures in the lower and middle areas are nerve trunks from which many branches ascend to supply the tactile spot. Here they break into fine threads that wind among the tactile cells and end as tiny bulbs or menisci on some of them. The group of tactile cells constituting the spot lies just beneath the epidermis. Between the tactile cells and the epidermis there is a narrow strip of corium which does not show in the picture, the section being very thick. Some nerve fibers continue upward across this strip and enter the epidermis. According to Plate (1924, pages 61 and 63), the meissnerian corpuscle of human skin is a direct evolutionary form of these reptilian tactile spots.

FIG. 8. Tactile spot from the palate of the alligator. There is no pigment, although the stratum corneum of the epidermis has blackened in the silver, except over the tactile spot. Beneath this rounded elevation there is a group of tactile cells with many delicate nerve fibers winding among them and ending on some of the cells. Between the tactile cells and the epidermis there is a broad band of colorless corium. Some of the nerve fibers cross this space to enter the epidermis. Below a large nerve trunk branches upward, sending three bundles to supply the tactile spot.

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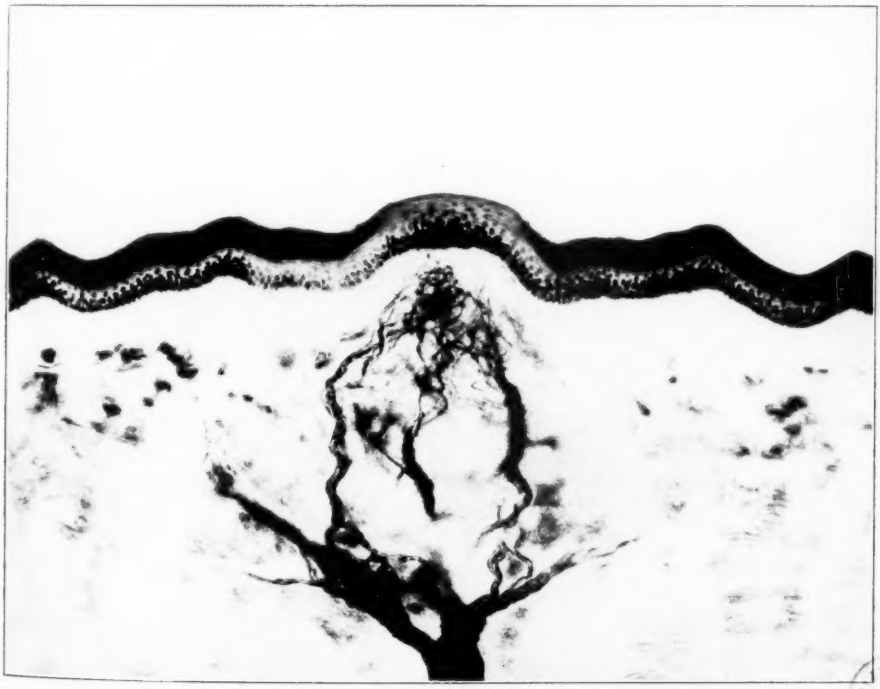

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THE CYTOLOGY OF THE GLIOMA GROUP; WITH SPECIAL REFERENCE TO THE INCLUSION OF CELLS DERIVED FROM THE INVADED TISSUE *

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INTRODUCTION

In the histological study of the material to be described in this paper the writer was impressed by certain difficulties in identifying individual cells, difficulties that many writers have ignored or have touched on but lightly. The chief source of these difficulties was the persistence within the tumours of included normal brain elements or of reaction forms derived from them. The included non-neoplastic elements were most frequently astrocytes or their derivatives, and less frequently nerve cells and fibres.

The study of these included elements, though at first sight of little importance, is nevertheless essential to correct interpretation of the histogenesis of the tumours. The nature of certain tumour cells may be suggested by the presence of more differentiated forms in their vicinity, and it is imperative, therefore, to determine whether these forms are merely included non-neoplastic elements or whether they are indeed tumour cells derived from or producing the less differentiated cells.

This paper, the aim of which is to study the nature and history of the individual cells rather than of the tumours as such, is divided, therefore, into two parts. In the first, those cells that appear to be truly neoplastic are described and discussed. In the second, certain observations on the reaction of the invaded tissues are recorded, and the relation of this reaction to inclusion forms within the tumour zone is discussed.

In order to do this it is necessary to accept some form of tumour classification as a basis. The Bailey-Cushing classification of 1926 [1] is admirably suited to this purpose, as it embraces names that have been widely accepted in the English-speaking world. This classification will probably be considerably modified in the future. It pos-

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sesses certain minor disadvantages, but at present it has the great advantage of being the common language of many neurologists, neurosurgeons and pathologists. The value of its conception can hardly yet be appreciated. Based on an unrivalled series of cerebral tumours it forms a great landmark in the history of the study and classification of the glioma group.

The specific impregnation methods of Golgi, Bielschowsky, Cajal, and del Río-Hortega were employed by Bailey and Cushing in their study of gliomata. In 1926 they produced their monograph. In it they adopted a classification based on histogenesis, and divided these neoplasms into fourteen categories. The majority of the types had been previously described, but to them they added the important, if uncommon, group of the oligodendrogliomata.

They sought in each of their large series of tumours representatives of the various embryonic or adult types. Where a tumour occurred which seemed to contain a predominance of some particular cell, they named that tumour accordingly. The nature of these cells was deduced from a study of their form, their affinity for various stains, and the appearances of the more adult forms in their vicinity.

Such a classification based on embryogenesis has been applied to tumours elsewhere. It is doubtful if in a pure form it is entirely satisfactory. There are also certain features of this particular classification that require some consideration.

1. From Bailey and Cushing's presentation of the subject the impression is gained that these authors assume that tumours arise from cells that have suffered arrested development. Bailey has recently disclaimed his belief in such a theory [2] and states that the most he has done is to give names to the tumours chosen from the histogenesis of the nervous system, because the cells of the tumours seem to resemble in their structure these embryological forms. In the classification this is not made clear. The tumour cells are usually described, with the exception of those of the spongioblastoma multiforme, as *being* such cells, not as *resembling* such cells.

At the same time the theory of embryonal rests and the origin of tumours from heterotopias is seriously discussed. There is undoubtedly a certain amount of evidence to suggest that errors of development may be associated with cerebral tumour formation. Thus the medulloblastoma of the cerebellum has been noted to occur in twins. Retinal neurocytoma, a similar tumour, is frequently bilateral and

familial. Neurofibromatosis may be associated with gliomata in the region of the optic chiasma or even, as in a case described by Schnyder, with a circumscribed glioma in addition.[3]

In Lindau's disease various developmental defects are associated at times with a cerebellar haemangioblastoma, while the cerebellar ganglioneuromata have been noted to occur in association with various developmental deformities. In this series an oligodendroglioma was associated with numerous small subependymal nodules, although these could not be said to be truly neoplastic.

The frequency of the occurrence of tumours about the fourth ventricle of young subjects is also held to indicate an origin from cell rests, as in this area heterotopias of various sorts have been observed.

When we consider the tumours of later life, and in particular the so-called spongioblastoma multiforme, we find little evidence to support such an origin, although this is contrary to the view held by Globus.[4] Bailey and Cushing were always uncertain of the origin of this tumour as they had observed its differentiation from the protoplasmic astrocytoma. Now Bailey [2] speaks of its constituent cells as anaplastic cells. He prefers the non-embryogenetic name of glioblastoma.

The cells of glioblastomata possess every characteristic peculiar to anaplastic tumours, that is, to tumours composed of undifferentiated cells derived from more adult elements. Polarity of the cells is largely lost, and they possess abundance and abnormality of mitotic figures. Moreover, such tumours have been observed to be derived from such well differentiated tumours as the astrocytomata, this change in characteristic not uncommonly following operative interference.

If we are confronted with a section containing astrocytes and less differentiated forms, and we are assured that such astrocytes are not included, there are two possibilities, *viz.*, the astrocytes may be differentiated from the less differentiated forms, or the less differentiated forms may, by the process of anaplasia, be derived from the astrocytes.

Roussy, Lhermitte and Cornil have clearly recognised the difficulties of the Bailey-Cushing classification. Roussy [5] remarks that they would prefer to class tumours of the nervous system according to their objective structural aspects and their predominance, with-

out seeking to draw from morphology deductions of an embryological or histogenetic order, which are far from being demonstrated.[5]

Ewing,[6] in speaking of tumour classification in general, summarises the situation: "The generally accepted plan of classification and terminology which is based on histology, modified as much as possible by histogenesis, is a natural product which has become very firmly established, and probably deserves to prevail against the varying prominence of embryology, chemistry and etiology."

2. Another difficulty of this classification arises when we examine certain individual tumours. Even if we believe that the cells of a tumour are embryonal in type, it is not always possible to be sure which cell type they represent. This is exemplified by the unipolar spongioblastoma of Bailey and Cushing. As the name suggests, they regard the cell type of this tumour as a unipolar spongioblast or precursor of the astrocyte line. Josephy,[7] however, described this tumour as a *neurinome centrale*, on account of its striking resemblance to the common auditory nerve tumour. Roussy and Oberling [8] believe it to be composed of oligodendroglial elements, while Courville [9, 10] sees in it an immature ganglion cell tumour.

The so-called medulloblast is another difficulty. Bailey and Cushing find glial and neuronic elements within medulloblastomata and so liken the cell type to the hypothetical undifferentiated cell of Shaper, which may differentiate along either line. Penfield [11] does not find neuroblasts and considers the medulloblast to be an apolar spongioblast. Roussy and Oberling [8] would prefer to use the term neurospongioma for the tumour, as they have found a fine groundwork of neurofibrils in certain of their examples. Ewing [6] classes it under the neurocytomas. Ribbert [12] describes a tumour that may be of this type with unusually well marked rosette formations and likens it to the rare suprarenal neuroblastoma.

3. In the Bailey-Cushing classification it is usually assumed, as already stated, that more adult forms occurring with less differentiated elements are derived from the latter. Even if this could be accepted, we are yet faced with another practical difficulty. A glioma is a glial formation invading glial tissue, and it may be extremely difficult to determine which are the invading cells and which the cells of the invaded tissues. It must be remembered that the glioma is usually only locally malignant, and, except in a few implanted secondary tumours recently described by Russell and

Cairns,[13, 14] we have few examples of the appearance of such tumours in an unrelated tissue.

This point is of importance as many authors base their view of the nature of the more immature forms on the undoubted histological nature of the adult forms. It is true that the gap between is always said by them to be bridged by intermediate forms, but even this appearance at times may be misleading.

In my experience included astrocytes may mimic spongioblasts, astroblasts and giant cell forms, and included neurones may present the appearance of neuroblasts. Only a close study of the tumour edge and the neighbouring invaded area will solve the mystery of many of these forms. A small biopsy portion removed at operation may be entirely misleading.

This criticism does not suggest that many of the excellent names used by these authors should be discarded. Time and additional study will undoubtedly result in certain alterations that seem more appropriate. In the process of modification there is no necessity to keep to names with an embryogenetic significance. By doing so one is apt to convey an incorrect idea of the nature and evolution of the tumours.

The Bailey-Cushing classification has been of the greatest utility to the neurologist and the neurosurgeon. It has focussed attention on tumours of heterogeneous appearance and has resulted in the recognition of definite clinical types of tumours, with definite natural histories and methods of treatment.

Since the original subdivision into fourteen categories simplifications have been introduced. Minor differences of structure, as, for instance, the distinction between ependymoblastoma and ependymoma, have been discarded for practical purposes. In a later publication Bailey [15] has reduced the categories to ten. Thus the two types of astrocytoma have been fused (Cushing,[16] Penfield [17]), and the pineoblastoma has been included with the medulloblastoma.

Roussy and Oberling [8] have recently introduced a new and instructive classification. Its main distinction is that certain cells, regarded by Bailey and Cushing as embryonal, are considered by them to be of an adult nature. The apparent embryonal form indicates to them a degenerative change. Thus they describe several varieties of glioma, a term applied in their classification to any tumour composed of adult astrocytes. The differences in appearance are

described in more detail than is usually given, and although they accept most of the tumour types described by Bailey and Cushing they discard one, the astroblastoma, as representing a degenerate form of an astrocytoma. In addition, they are not entirely in agreement as regards the actual histology of other forms. This atlas is an extremely instructive and valuable work, and should be read in association with the Bailey-Cushing classification. Certain features are discussed later in this paper.

The simplest classification proposed is that of Carmichael.[18] It is essentially a practical subdivision into the more adult and the grossly anaplastic forms. The first he would call the spongioblastic group and the second the astroblastic.

Table I, somewhat modified from Brain and Strauss,[19] with additions, shows the relation of the many names applied to the gliomata.

Text-figure 1 represents the scheme of evolution of certain elements of the central nervous system, and will serve as a key to names commonly used in describing the histology of these tumours.

In this paper cells that are not truly neoplastic and are the residue of, or derived from, the invaded tissue are for the sake of convenience described as inclusion cells.

Methods

The material used has been a series of 120 intracranial tumours, including 70 gliomata, mainly obtained in the postmortem room. Most of these were obtained recently, but a number of valuable specimens have been obtained from pathological museums. The impregnation of these old specimens was usually extraordinarily good, except in the case of the gold stains.

Various areas of the tumours were studied, and in particular the growing edge.

The majority of specimens were preserved in formalin. The method of Davidoff [20] was occasionally used for reimpregnation with Zenker's fluid. Isolated examples were put directly into Zenker's fluid or into formol bromide. Some of the older specimens may have been originally preserved in spirit, but were in dilute formalin at the time of examination.

Paraffin sections and frozen sections were used together in most cases. The methods employed as the occasion demanded were:

TABLE I

Bailey and Cushing	Bailey (1927)	Roussy and Oberling (1931)	
1. Medulloblastoma	1. Medulloblastoma	Neurospongiome	Neuroblastoma (Wright) Neurogliocytome embryonaire (Masson) Glioma sarcomatoides (Borst)
2. Pineoblastoma			
3. Neuroepithelioma	2. Neuroepithelioma		Neuroépithéliome (Flexner) Retinocytome à stephanocytes (Mawas) Blastome ependymale (Marburg)
4. Spongioblastoma multiforme (glioblastoma)	3. Spongioblastoma multiforme (glioblastoma)	Glioblastome	Spongioblastoma multiforme (Globus and Strauss) Glio-sarcoma (Ewing, Borst) Gliome à petites cellules (Masson) Gliome polymorph (Roussy, Lhermitte and Cornil)
5. Pinealoma	4. Pinealoma		Pinealoma (Krabbe) Chorioma (Askanazy) Compound pineal gland type (Strong)
6. Spongioblastoma unipolare	5. Spongioblastome unipolare	Oligodendrocytome fasciculé	Neurinome centrale (Josephy-Macpherson)
7. Astroblastoma	6. Astroblastoma	(Included in astrocytomas)	Neuroblastoma? (Greenfield)
8. Ependymomas 9. Ependymoblastoma	7. Ependymoma	(*a*) Ependymocytome (*b*) Ependymoblastome (*c*) Ependymogliome	Ependymal glioma Glio-ependymome (Masson)
10. Astrocytoma fibrillare	8. Astrocytoma	Astrocytome	Astrocytoma (Ewing)
11. Astrocytoma protoplasmicum			Sternzellen (Stroebe)
12. Oligodendroglioma	Oligodendroglioma	Oligodendrocytome	Gliome à petites cellules rondes (Roussy, Lhermitte and Cornil)
13. Ganglioneuroma	Ganglioneuroma		Neurogliome ganglionaire

1. Paraffin sections: Haematoxylin and eosin.
Haematoxylin and Van Gieson.
Mallory's phosphotungstic acid haematoxylin.
Weigert's iron haematoxylin.
Nissl's method.

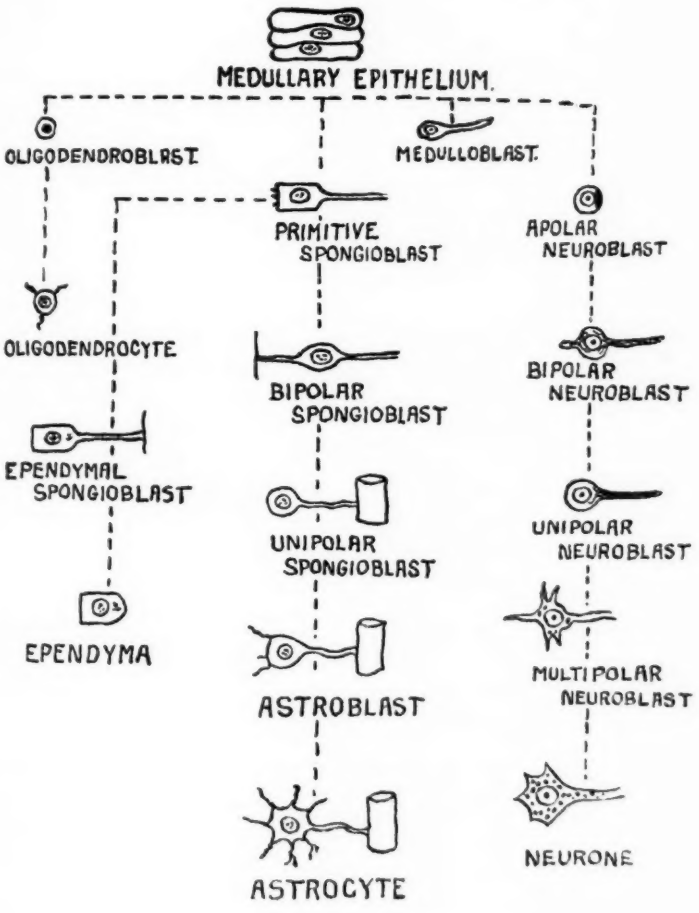
2. Frozen sections: Haematoxylin and eosin or Van Gieson.
Cajal's gold sublimate stain — after formol bromide or more usually following the Globus-Penfield technique.[21, 22]
Cajal's pyridine silver method.
Hortega's fourth variant.
Hortega's method for oligodendroglia and microglia following the Cone-Penfield modification.
Bielschowsky's method for frozen sections.
Weigert's medullary sheath stain.

In ordinary postmortem material, as received in the Baker Institute, it was soon realised that the metallic stains were only specific in a comparative sense. In this regard gold sublimate was perhaps the most satisfactory and rarely provided any impregnation of cells less mature than those at a well formed polar stage. Included astrocytes and their modifications were, however, usually clearly impregnated. The very old tumours, with occasional exceptions, did not impregnate satisfactorily. One tumour nearly 30 years old gave a fair impregnation, while certain more recent ones were unsatisfactory.

The silver pyridine stain of Cajal was originally considered specific for neuroblastic forms, and in the first classification deductions were made as to the nature of cells based on this specificity. Bailey later discovered that this was not entirely so. In the experience of this laboratory normal neuroglia was rarely impregnated, although any large hypertrophic forms, whether neoplastic or about the tumour edge, might be. Many astroblastic forms, as well as polar and asteroid forms, were at times densely impregnated. The older the material, the less specific this stain seemed to be. The polar cells of an ependymoma, which had been preserved for 37 years, were densely impregnated.

The combined method for oligodendroglia and microglia astonished the author by impregnating some of the oligodendroglial cells in an undoubted oligodendroglioma that had been preserved for 28 years.

The silver carbonate method often gave excellent impregnation of nerve inclusions, as well as astroblastic and asteroid forms, particularly if the sections were deliberately overstained.



TEXT-FIG. 1

Illustrating the terminology of embryogenesis of the cell elements of the central nervous system, as applied to cells of somewhat similar appearance and staining reaction in the gliomata.

PART I

MEDULLO-EPITHELIOMA

It is appropriate to commence the discussion of the individual tumour groups by considering the very rare medullo-epithelioma. Bailey and Cushing place this at the head of their classification, as it represents to them the arrangement of the medullary epithelium, the first indication in the embryo of the developing nervous system.

Such a tumour consists of bands and folds of columnar cells, with oval nuclei, possessing well marked external and internal limiting membranes. They have observed two examples, one arising in the postinfundibular region, and the other in the midbrain. Mitotic figures were numerous, and each tumour presented appearances suggesting considerable malignancy.

The only positions where the embryonic formation of the medullary epithelium is retained as an adult structure are in portions of the floor and the roof palate of the third ventricle, and in the epithelium covering the pars ciliaris retinae. Tumours that arise in these regions may be expected to reproduce something of the structure of the tissue of their origin. As this tissue is no longer an embryonic but a fully differentiated tissue, it should not be expected to reproduce the full range of cells, neuronic and glial, for which the medullary epithelium is responsible. It should be expected to give origin to tumours, some of slow and some of rapid growth, reproducing more or less accurately its own structure, much as does any other adult tissue. The analogy with medullary epithelium is misleading.

In this series a small defined tumour about 1 cm. in diameter was encountered in the midline of the infundibular region. Its consistence was firm, a small cyst occupying its centre. Section showed an arrangement of columnar cells presenting somewhat the appearance of the medullo-epithelioma (Fig. 1). Mitotic figures were not observed, its appearance being essentially non-malignant.

This group of tumours in the cerebrum is extremely rare and no definite opinion can yet be expressed concerning them.

The retinal examples have been recently summarised by Grinker[23] and may be studied in his paper.

Neuro-Epithelioma

Flexner [24] in 1891 described a tumour of the retina, for which he chose the name neuro-epithelioma. Other examples have been described, and they have been recently epitomised by Grinker.[23] He adds a further example which he has studied by the full modern histological technique.

The tumour cells tend to arrange themselves into true rosettes, with well defined lumina. Cilia may be observed projecting into the cavities and blepharoplasten are usually seen in the neighbourhood of these cilia. The outer extremities of the cells stream into the neighbouring tissue as tail-like processes which may be attached to neighbouring vessels. The whole form and general arrangement strongly suggest the arrangement of the primitive spongioblasts into neuro-epithelium. Certain non-malignant excrescences of similar structure may appear in relation to the senile ciliary body, or even in infections of the same region, and the resemblance of these cells to normal rods and cones, themselves derived from primitive spongioblasts, has been commented upon.

Tumours of this nature are extremely rare in the brain, no example occurring in the original Bailey-Cushing series. They have been observed in the brain, in the spinal cord, and in the sacrococcygeal region.

Bucy and Muncie [25] have recently reported a tumour of the cerebellum which appears to be of this nature. They accept only five other examples, one occurring in the cerebellum (Naeslund's case), one in the frontal lobe (Bailey [15]), one near the sylvian aqueduct (Roussy, Lhermitte and Cornil[5]), one in the left cerebral hemisphere (Ribbert [12]), and an unpublished case of Cushing's occurring in the fourth ventricle. They classify other reported examples, with one possible exception (Nyematsus' case), as being ependymomata or ependymoblastomata.

It must, however, be realised that adult cells of the appearance of the primitive spongioblast occur in such regions as the anteromedian fissure, the posteromedian septum of the spinal cord in the median raphé of the hind brain, as well as in the rhombic lip of the fourth ventricle.[26] Also very similar cells may be observed in the ependyma-lined clefts of the ependymoma (Fig. 2). The distinction then be-

tween the neuro-epithelioma and the ependymoma may be more apparent than real.

For a tumour to be composed of true neuro-epithelium, as opposed to an adult structure of similar appearance, one would expect, as Roussy and Oberling suggest,[8] evidence of differentiation into spongioblastic and neuroblastic forms. This is not usually evident.

Many of the reported cerebral neuro-epitheliomata do not suggest any great evidence of malignancy. Even those of the retinal type, although showing more evidence of mitotic division, are among the less malignant tumours of this region.

Medulloblastoma

This very characteristic tumour occurs predominantly in the mid-cerebellar region in childhood, but may occur in the cerebrum and in adults. The typical cell is small and strikingly uniform in appearance (Fig. 3). In paraffin sections the cytoplasm is indistinct, but in preparations stained by the supravital technique it is very clearly stained and delimited.[27] The nucleus, which is round, oval or occasionally elongate, possesses a dense chromatin network and may show mitotic figures. Such cells at times arrange themselves in rosette formation; the cytoplasm may be carrot-shaped, with a tail streaming toward the centre of the rosette.

Bailey and Cushing named this cell a medulloblast, on account of the occurrence of both spongioblasts and neuroblasts within these tumours. A capacity to differentiate in each direction suggested to them the theoretical medulloblast of Shaper, which is credited with this ability.

At a somewhat later date Cushing [28] revised this description. The cerebral medulloblastomata were found to occur at a later period of life, to be slower in growth and to have differentiated more fully. It is in this type that most of the described neuroblasts and spongioblasts occur, but Bailey [15] finds cells that he believes to be neuroblasts in the cerebellar type.

Roussy and Oberling [8] liken the appearance of this tumour to the neurospongium, that is, to the appearance of the primitive neural epithelium, when the germinal cells have separated and are in active subdivision. The fine fibrillary network so common is to them a network of neurofibrils. They find neuroblasts and their progeni-

tors to be constituents of these tumours and distinguish two forms, a *neurospongiome essentiellement neuroblastique* and a *neurospongiome neurospongioblastique.*

Penfield [11] finds spongioblasts, but no neuroblasts. As a medulloblast has never been observed in normal histology he considers this cell an apolar spongioblast.

There is a great likeness of this tumour to one tumour described as glioma of the retina. When the latter invades the cerebrum, as it did in a recent case reported by Cairns and Russell,[14] the appearance seems to be entirely similar. Both of these tumour types usually occur in the early period of life.

The polar forms that occur in this condition are interesting (Fig.4). They are common in the cerebral examples and their extremities fray out into a fine fibrillar substance. Cairns and Russell report a case where polar cells occurred in the cerebellar type. The processes were clearly stained with Mallory's stain, thus suggesting their relation to the astrocyte series. The history of this tumour was unusually long, covering a period of 6 years. However, in two cerebellar examples recently examined in this laboratory, in which polar cells predominated, the courses were exceedingly brief.

A cerebral example occurred in this series in a child. The growing edge presents two distinct appearances, one corresponding to the ordinary appearance of the medulloblastoma, and the other to the polar type. In each of these areas mitotic figures are equally abundant, and there is nothing to suggest that the polar cells have differentiated from the apolar.

The polar forms at the growing edge show nuclei of almost a cigar shape, the cells being disposed in clumps and often presenting an appearance of palisading. The marked fibrillary formation separating these clumps may be distinguished clearly in haematoxylin-eosin preparations. From each clump streams a band of parallel fibrils, which are interwoven with similar strands from other areas. These cells present no suggestion of being neuroblastic, and seem more allied to the astrocytic series. At the same time, the description of them as spongioblasts seems hardly applicable. A similar tumour is figured in Roussy and Oberling's atlas.

Eight cerebellar cases were examined, six occurring in young children and two in adults. Considering that the average life in Cushing's cases was about 1 year from onset, three of these cases

presented unusually long histories. In one, a child 11 years of age, signs of internal hydrocephalus had been present for over 5 years. The history in the second case, in which dissemination over the cerebrospinal axis was wide, extended over $3\frac{1}{2}$ years, and that of the third for over 2 years. In the case with the longest history mitotic figures are few and polar forms are rare. No spongioblasts or neuroblasts are observed, but there is a remarkable preservation of nerve fibres in the tumour substance. There is also a well marked astrocytic stroma, without any suggestion of intermediate forms between astrocyte and medulloblast. In the third case a similar appearance is observed, but more mitotic figures are present. The remaining examples, with one exception, are much more highly malignant and mitotic figures are numerous. In one example the nuclei frequently present a single large nucleolus and a comparison with the nuclei in the neighbouring granular zone of the cerebellum shows a remarkable similarity. This type of nucleus is, however, not uncommon in rapidly growing tumours. Moreover, silver impregnation shows no impregnation of the intercellular network, although climbing and mossy fibres in the neighbouring cerebellar zone are well impregnated.

There is no evidence in these tumours of the occurrence of neuroblasts, even in the more slowly growing types where this might be expected to occur, but there is a certain amount of evidence that such tumours may evolve forms suggestive of the astrocyte series.

There is always considerable difficulty in determining which cell these small-celled embryonal tumours represent (Ewing [6]). My limited experience somewhat favours the view held by Penfield. It must be admitted that a slide of the small-celled embryonal tumours of the kidney could easily be transposed for a medulloblastoma without detection.

General Conclusions

1. The so-called medulloblast is possibly a cell of embryonal type, according to the definition of Ewing.[6] Exactly where it stands in histogenesis could not be determined by any observation made in this series.

2. At times it assumes an elongate form with numerous fibrillae. Although this usually indicates a less malignant tumour, it does not necessarily do so, as some forms may show active mitosis. It may

indicate a tendency to form an astrocytic type of cell of polar form.

3. The cell type is usually very constant. Such cells may be in active subdivision, or again, the tumour may be comparatively slow in growth, as shown by little evidence of cell division.

4. No evidence of the presence of neuroblasts was noted in these tumours.

Spongioblastoma Multiforme — Glioblastoma — Gliosarcoma

This very common tumour occurs predominantly in the cerebral hemispheres in the middle decades of life. The older name, gliosarcoma, was applied by Stroebe under the belief that the vascular hyperplasia participated in the tumour process. Ewing, with Lubarsch and Adami,[6] still finds no real objection to the name.

The name spongioblastoma was introduced by Strauss and Globus [29] and Ribbert [12] in the same year. The former authors, in a later paper,[30] described sixteen cases and presented most of the essential cell elements to be found in these tumours.

The name was accepted by Bailey and Cushing, although Bailey [15] at a later date wrote that they did so with some diffidence and would prefer the name glioblastoma.

Penfield objects to the name glioblast, as there is no such cell in normal histology. One might suggest that this is *not* a *disadvantage*, as these cells are not normal cells but anaplastic tumour cells. It seems better to use a general name, rather than one employed in normal histogenesis.

The glioblastoma possesses every feature that Ewing regards as necessary to discriminate an anaplastic from an embryonal tumour. It is extremely cellular, departs in type from the cells from which it is derived, mitotic figures are abundant, and areas of cells are usually present which have entirely lost their polarity.

Tumours of this type have been observed to arise from tumours regarded as astrocytoma (Tooth,[31] Globus and Strauss,[30] Bailey and Cushing [1]). Globus and Strauss found evidence of tuberose sclerosis in three of their cases, and multiple tumours have also been reported. It is probable that the ordinary clinical type is derived from adult elements.

Tumour mixtures are frequent; areas of astrocytoma, ependymoma, astroblastoma and other varieties are encountered. In this series areas of glioblastoma occurred in association with formations of the nature of astrocytoma, astroblastoma, ependymoma, polar spongioblastoma and again in a tumour that was present in the position of the pineal gland. Bailey and Cushing appear to assume that the more adult cells are differentiated from the less differentiated. This assumption must be accepted with considerable reservation. In many of my cases the appearance was such as to suggest that a more differentiated tumour had become anaplastic.

A large tumour was encountered occupying the lateral ventricle of a man 65 years of age. The structure in parts is undoubted ependymoblastoma. At one extremity this embryonal appearance is entirely lost, the tumour has assumed the anaplastic appearance of the glioblastoma and has become adherent to the tentorium in which it was actively growing. In the midline of the cerebellum another tumour of undoubted ependymal nature occurred, but without any suggestion of anaplasia.

On the other hand, certain tumours included in this group do not present such marked evidence of anaplasia. One tumour is composed almost entirely of small unipolar cells taking the gold stain intensely. Mitotic figures are not evident, and the general appearance is that of three tumours described by Carmichael[18] as spongioblastoma unipolare. Possibly this group should be separated from the glioblastoma group. The name spongioblastoma unipolare would have been admirable if it had not been already applied to an entirely dissimilar tumour.

If all the forms encountered within this tumour group were described we should have a description of the majority of cells occurring in the gliomata as a series.

Before such a description is attempted it would be well to mention briefly a very constant feature, the extraordinary proliferation that may occur in the walls of the vascular channels. This hyperplasia involves both endothelium and adventitia, but it is the remarkable multiplication of the endothelial cells that is most characteristic. Stroebe, as previously noted, regarded this change as part of the tumour process, and Penfield[17] has recently expressed the view that it may yet prove to be the essential part of the tumour. Certainly the endothelial proliferation may be observed well beyond

the tumour edge. However, at times a somewhat similar appearance may be noted outside the edge of a metastatic carcinoma nodule. Cairns and Russell [14] have also found similar changes in the vessels of the meninges, where a fragment of glioblastoma had become implanted and was in active growth.

The following cell types, which appeared to be of a true neoplastic nature, were noted:

1. The most constant cell type is of rounded, ovoid or irregular shape. The protoplasm is usually ample, the nucleus clear and vesicular, while mitotic figures are frequently encountered. The size of nucleus and cell is extremely variable, and all transitions occur between such cells and giant cells of great size (Text-fig. 2A). It is apparent from the description of this cell type that it might fit equally well an anaplastic cell of non-glial origin. This is the common and characteristic cell. It may be the only cell type present, and possesses no specific staining properties.

2. Giant cells are usually present. In one tumour they form the predominant cell. Some are of enormous size, and possess either one large single nucleus or numerous nuclei containing various atypical arrangements of the chromatin. These cells again possess no properties peculiar to glial cells. It is not unusual to find a large chromatic sphere centred in the nucleus. Such cells could easily be mistaken for the neuroblastic cells, but they possess little affinity for either silver or gold stains (Text-fig. 2B and Fig. 6).

3. It is frequently found, even with ordinary aniline stains, that the undifferentiated cells, as described above, arrange themselves radially about areas of necrosis or vascular channels. They then assume the polar form, which is commonly described as that of the bipolar spongioblast. In general, such forms do not present the intensity of staining reaction to gold that occurs in the more organised cells of this form. However, it is possible that this appearance represents some differentiation of an early order.

4. At times bipolar forms of a more highly differentiated order occur about vascular channels. The processes are fairly thick and show a marked affinity for the gold stain. In appearance they are quite similar to the spongioblastic cells occurring in the ependymal tumours, and in one tumour occurring in a frontal lobe areas quite indistinguishable from the ependymoblastoma are present. It must be remarked that mitotic figures are scanty in this tumour, and it

is possible that it may be an anaplastic ependymoma occurring in an unusual situation (Text-figs. 2D and E).

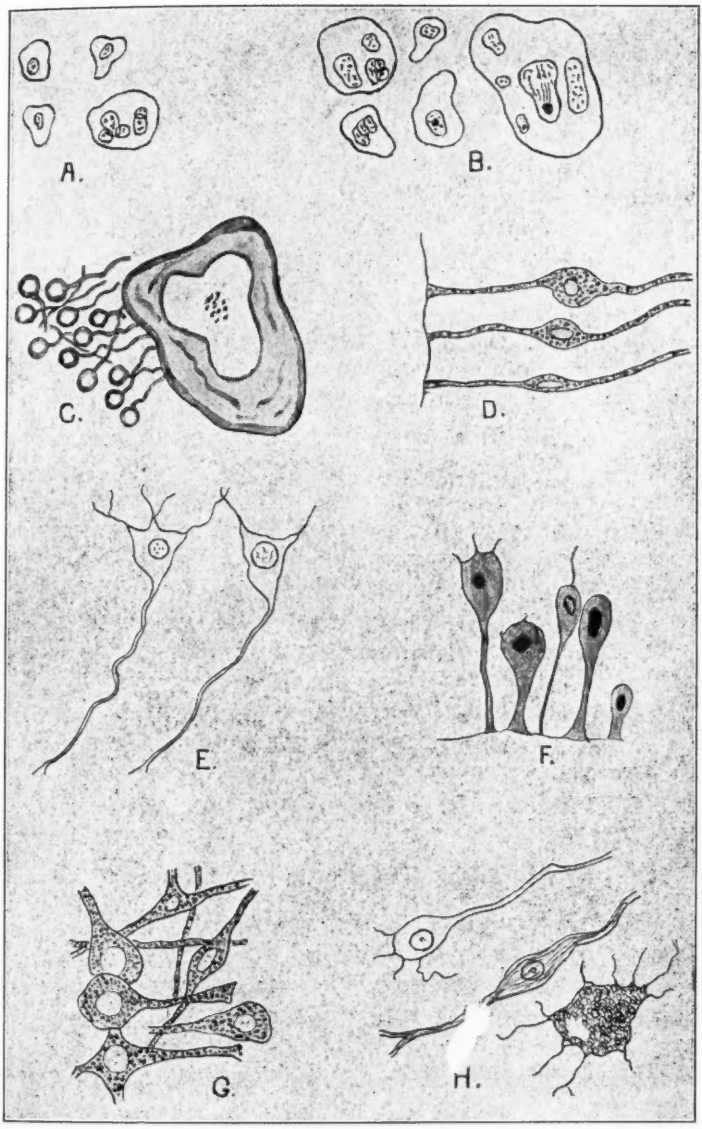
5. In five tumours astroblastic forms are prominent, and it becomes difficult to be certain under which category such a tumour should be placed. In three, however, the vascular response and frequency of mitotic figures indicate the glioblastoma.

The astroblast of normal histogenesis is a very typical cell. According to de Castro [32] a bipolar spongioblast secures a vascular attachment by one pole. This process hypertrophies and widens to a bell-shaped area at the point of attachment, while the other process atrophies. This formation marks the so-called astroblast. Fine processes emerge from the end distal to the blood vessel and thus gradually the adult astrocyte with its vascular attachment is formed. In the astroblastic stage glial fibrils have not differentiated.

Although the same type of cell is achieved in one of the above tumours the process of development is at times different. It commences as a columnar cell firmly set into the vessel wall, the nucleus being in that part of the cytoplasm distal to its attachment. The cell elongates, and by a constriction of the protoplasm near the vessel produces the first evidence of its vascular attachment and of its sucker foot. By a migration of the nucleus and its protoplasm still farther away, and with the formation of fine distal processes, the astroblastic form is assumed (Text-fig. 2F and Fig. 6). Such cells impregnate well with the metallic stains. Gold sublimate stains them brilliantly, but the silver carbonate methods show the cell form with more detail (Text-fig. 2E), while Cajal's pyridine silver is also effective in demonstrating them. They often present an extraordinary similarity to nerve cells and were, in fact, labelled provisionally by Greenfield [33] as neuroblasts.

6. One tumour was found to be almost entirely composed of small cells, mainly of unipolar form. They stain selectively with the gold sublimate stain and present an appearance analogous to the unipolar spongioblast of histogenesis. They are much smaller than the bipolar or astroblastic forms previously described, but possess a fine vascular attachment (Text-fig. 2C and Fig. 7). The name spongioblastoma unipolare, as previously noted, would have been eminently suitable.

7. Certain of the tumours show numerous bipolar cells of an entirely different type from those already described. These cells will



TEXT-FIG. 2

Drawings of various cell types occurring in the glioblastoma multiforme and in the astroblastoma. A. Outline of anaplastic cells from a haematoxylin-eosin preparation. B. Outline of giant cells from the same tumour as Fig. 6. Haematoxylin-eosin. C. Small unipolar cells showing the relation of the processes to a thickened vessel, from the tumour shown in Fig. 7. Gold sublimate. D. Bipolar cells of the type seen in the ependymoblastoma. Gold sublimate. E. Outline of so-called astroblasts. Silver carbonate. F. The transition between a columnar cell set in a vessel wall and the astroblast. G. Various cells occurring in the astroblastoma shown in Fig. 10. Many of these cells resemble swollen protoplasmic astrocytes. H. Cells of the same tumour. Silver carbonate stain.

be described in more detail in the discussion of the polar spongioblastoma. The processes are long and frequently run in bundles, but the cells do not exhibit the special tendency exhibited by the other polar forms to radiate from or to be attached to vessels by these processes. On closer observation the polar expansions are frequently seen to break up into several strands. Many of these processes stain with Weigert's iron haematoxylin or Mallory's phosphotungstic acid haematoxylin stain, and the impression is gained that we are approaching an adult astrocyte cell of the polar, or of the piloid, type.

8. In certain tumours it was found difficult to separate the individual cells, despite the various staining methods employed. The appearance is that of a syncytium. These are all highly cellular gliomata, some with the vascular response of the glioblastomata, others resembling more a highly cellular astrocytoma. Bailey and Cushing regard the syncytial appearance so common in the glioblastoma as evidence of degeneration. In my experience this is not always so. In one example, which appears to be entirely of this nature, there is a remarkable preservation of neurones. The gold sublimate stain often impregnates this syncytium well. This appearance was common in gliomata in the region of the brain stem, although one occurred in association with a cyst on the basal ganglia of a child of 10 years.

Reynolds and Slater,[34, 35, 36] in their studies of the gliomata, have paid some attention to this appearance. In a study of fifteen gliomata, they found thirteen fairly actively growing tumours. The edges of two appeared to be composed of a syncytium from which individual cells later separated. In three cases the gliomata were entirely syncytial, one having a history of over 4 years duration. They found all grades of differentiation between syncytium and astrocyte, but were uncertain whether the large astrocytes of the tumour could of themselves divide.

The syncytial appearance will frequently resolve itself in a remarkable way with the special stains. Thus, the small unipolar tumours described appear in paraffin sections to be entirely syncytial. There may also at times be observed in the astrocytomata syncytium-like areas, which, when impregnated with gold sublimate, are clearly not astrocytic, and these probably represent undifferentiated tumour cells. The syncytial tumours of a highly cellular

order, in my experience, contain fewer mitotic figures and a better preservation of glial and neuronic elements than the highly cellular glioblastoma.

Summary: 1. The glioblastoma is best considered as a locally malignant anaplastic tumour.

2. It may be associated with, and is possibly derived from, more adult tissue, for example, glia or ependyma.

3. Such cells may remain entirely anaplastic in character, or may assume in different degrees the more adult character of a spongioblastic, astroblastic or asteroid form.

4. At times the tumour cell may not de-differentiate to the apolar stage. The cells may be considered to multiply at an astroblastic, asteroid or polar stage.

5. The type composed of small unipolar forms is of different appearance from the ordinary type. This difference in form must not be interpreted too strictly in an embryogenetic sense. Chemicophysical agencies, such as pressure, oxygen starvation, and the presence of the products of necrosis, may have much to do with the shape and size assumed by the neoplastic cell.

6. It may be said that as a general rule tumours relatively rich in the more differentiated forms possess fewer mitotic figures than the less differentiated, but this rule is by no means absolute.

7. In some tumours the appearance of a syncytium is retained despite the use of special stains. Such a tumour is not of necessity degenerative.

Astroblastoma

This name is reserved for tumours in which so-called astroblasts are present in quantity. The characteristic appearance is that of numerous cells, each possessing one large single process of variable length which is either attached to a vessel wall or to a septum of connective tissue. The tumours are, on the one hand, related to the glioblastoma and, on the other, to tumours composed largely of protoplasmic astrocytes. They are tumours of the cerebral hemispheres of adult life, usually of diffuse type, and usually show degenerative changes. The average survival period of the Bailey and Cushing series of thirteen cases was 28 months. They are, therefore, slower in growth than the glioblastomata, but present some features in common.

Bailey and Bucy [37] have recently analysed twenty-five examples, besides giving an excellent general description of these tumours, and have also emphasised their inoperability.

The typical cell possesses a pyramidal body and a thick process attached to a vessel wall. From the other extremity of the cell fine processes may pass into the surrounding tissue, which frequently shows degenerative changes. These cells may be of asteroid or polar form and may show degenerative changes in the cytoplasm.

The origin of this type of cell has been discussed with the glioblastomata, where it often appears to be derived directly from a cuboidal cell, set in the vascular wall. However, such forms may arise by other means. Thus, degenerative changes occurring between the vessels lined by asteroid cells may result in a loss of all the processes except the vascular ones, and this appearance is not uncommon in the hypertrophied non-neoplastic astrocytes present at the advancing margin of a glioblastoma. Roussy and Oberling take this view of their origin and regard them, in fact, as being degenerated adult astrocytic forms. For this reason they decline to consider this tumour as a separate class, but rather as a degenerative type of astrocytoma. They note the appearance of similar cells in encephalitic lesions caused by radium.

It must also be noted that at times the large astrocytic forms present at the tumour edge may be introduced into a neoplasm as a vascular cuff, and produce a somewhat similar appearance (Fig. 8).

Tumours that fall within the category of astroblastoma are not all equally malignant. Some conform more to the glioblastic type, while others resemble the astrocytomata in their slow evolution. Thus, one of Cushing's cases gave a history of cerebral tumour existing over 15 years.

Three types of tumour have been described that might be included within this category:

1. Those examples that should probably be classified as spongioblastoma, of which four cases occurred in this series. A man, aged 29 years, developed signs of increased intracranial pressure and died within 4 months of the onset of symptoms. A small diffuse tumour was found deep within the left occipital lobe. Its general appearance was that of an undifferentiated, syncytium-like glioblastoma, but in certain situations these cells had, as previously described, formed definite astroblastomatous areas.

2. Type two is a very definite tumour type and corresponds to the appearance described by Bailey and Cushing. A woman, 47 years of age, presented signs of increased intracranial pressure. These rapidly progressed and death occurred after 5 weeks. A small, fairly well defined tumour was found at the junction of the right occipital and parietal lobes. Its edge was fairly clearly demarcated and its consistence somewhat greater than that of normal brain tissue. The tumour mass consists of areas of differentiated cells taking the gold stain intensely, set in massed form between dense connective tissue strands (Figs. 10 and 11). The main cell is large and pyriform, but with many bipolar and asteroid forms, while the cytoplasm of certain of these cells contains globular bodies that suggest degeneration. There is an entire absence of undifferentiated cells and mitotic figures cannot be observed. The cells border vascular areas, or connective tissue bands, and the tumour presents a general appearance of lobulation. The broad protoplasmic processes which pass from cell to vessel or stroma are often of considerable length in the deeply placed forms, and binucleated cells are not uncommon. Blood vessels are not numerous and degenerated areas are frequent in the central areas. The tumour cell, which is well shown by the gold stain, is clearly detailed by the silver carbonate method. The pyridine silver method results in impregnation of many of these cells, and one might well be excused for considering certain of them as neuroblasts. Fibrils can be seen in the cell protoplasm at times, but this is not a prominent feature. There is a considerable resemblance of these cells to those described by Roussy and Oberling in the *astrocytome giganto-cellulaire*.

3. Another type of tumour has been described as an astroblastoma, of which Carmichael quotes certain examples. These tumours seem, however, to be very closely allied to the astrocytoma and should possibly be included with them.

Summary: 1. The astroblastoma of Bailey and Cushing is a transitional type of tumour.

2. Cells of the appearance of astroblasts may be produced by a variety of means. Undifferentiated cells bordering vascular channels may pass directly into the astroblastic form without the intermediate spongioblastic form of histogenesis. Astrocytes may similarly, by a process of retrogression and possibly also by alteration in position, attain a similar appearance and arrangement about vessels.

3. The name astroblastoma should be confined to the type described by Bailey and Cushing. This may be regarded as somewhat intermediate between the astrocytoma and glioblastoma series.

4. In this series the majority of tumours composed mainly of so-called astroblastic cells showed numerous mitotic figures and were more closely allied to the glioblastoma. The two typical examples resembled more that type of tumour known as protoplasmic astrocytoma.

Polar Spongioblastoma

Bailey and Cushing examined examples of a tumour that they named a unipolar spongioblastoma. It was a firm, fairly well organised tumour of a much slower growth than the glioblastoma, the average survival period being 4 years. The site of election was the cerebellum of early years, but examples occurred elsewhere.

Microscopically, polar cells were found in an arrangement that suggested in low magnification an acoustic neurinoma. Between the cell bodies the tails ran in long, hard, wire-like processes, staining feebly with Mallory's phosphotungstic acid haematoxylin stain. Mitotic figures were rare.

That the so-called central neurinoma of Josephy is the same tumour is undoubted. The tumour is uncommon and the various authors who have encountered it have given almost every possible interpretation to the cell type. Bailey and Cushing [1] suggest that it may have attained this form through an attempt to differentiate along the lines of the neurilemmal sheath. Josephy [7] likens it to the acoustic neurinoma. Roussy and Oberling reason along the lines of the neurilemmal sheath.[8] As to the French school, the oligodendroglia is the representative of such cells in the central nervous system; they describe this tumour as an *oligodendrocytome fascicule.* Courville [10] suspects that the polar cell is an immature nerve cell. Penfield has found no neuroglial fibrillae in this tumour and believes it to be a spongioblast.[11]

It has been noted that, in the glioblastoma, areas of a somewhat similar appearance may occur. Penfield has remarked that this tumour is most often confused with the astrocytoma and must be distinguished from it by the absence of neuroglial fibrils. It has seemed to me that this type of tumour is midway between the glioblastoma multiforme and that type of astrocytoma in which fusiform or piloid cells are the prominent feature. Corresponding cells

occurring in the more organised type of glioblastoma multiforme have been noted previously.

A somewhat more organised type of tumour occurred in a child of 4 years, the survival period being only 4 months. The pons was largely replaced by a firm tumour, associated with a large central cyst. Microscopically, certain parts of this area present an appearance almost identical with that described by Bailey and Cushing. With the iron haematoxylin stain, in certain areas the dense stroma, in which the cells are set, shows many thick, well stained, wire-like processes (Fig. 12 and Text-fig. 3). Gold sublimate also shows the

TEXT-FIG. 3

Drawing of individual cells occurring in the tumour shown in Fig. 12.

cells clearly. Usually a large single fibril occurs in the tail of each cell. Other fibrils appear to be naked, but possibly possess a narrow protoplasmic sheath. However, other areas of this tumour show anaplastic forms, with many mitotic figures and giant cells, and are unquestionably highly malignant. In this tumour there is, therefore, a transition between what may be termed polar astrocytic forms, through polar forms without fibril formation, to ordinary anaplastic cells with giant cell formation.

A midline cerebellar tumour was examined in which polar cells without fibril formation are the prominent feature. There is no arrangement suggesting ependymoma and this tumour most closely preserves a pure spongioblastic form.

Another nodular tumour was examined in a woman 25 years of age. It apparently had arisen from the vermis and was growing into the mesencephalon. Although areas of this tumour are similar to

the description given of polar spongioblastoma, other areas are true astrocytoma of the fusiform or piloid type.

In a fourth tumour a firm nodular and lobulated mass had grown from the roof into the cavity of the fourth ventricle. The histological appearance is that of intersecting strands of fibres, and small and inconspicuous areas of polar cells (Fig. 13). This tumour is an undoubted astrocytoma of the subependymal type described by Roussy and Oberling.[8] It is similar in structure to the small, multiple, subependymal granules occasionally encountered and is described here, as there seems to be a transition between tumours of this type and the glioblastoma multiforme with polar cell formation. To me the polar spongioblastoma seems to be a halfway house. The nature of the astrocytoma composed of polar forms will be discussed later, but I would raise the question whether it would not be better to omit this group. The more malignant forms fall into the glioblastomata, and the less malignant, without much stretch of the imagination, could be included with the astrocytoma. The typical cell may represent an attempt to form an astrocyte of piloid type, as described by Penfield. Such cells are not uncommon in subependymal tissue.

Summary: 1. Tumours in which polar forms predominate are described.

2. The polar spongioblastoma of Bailey and Cushing is possibly an intermediate form between a glioblastoma with polar cells and an astrocytoma with cells of a fusiform or piloid type.

Ependymoma

Bailey and Cushing classed two types of tumours as arising from ependymal elements. In one group, consisting of five tumours, all of which arose from the floor of the fourth ventricle, the characteristic formation was an arrangement of well formed bipolar cells about thin-walled vascular channels.

The haematoxylin-eosin appearance was characteristic. Between a central vessel and a zone of nuclei lay a clear area, which consisted of those processes that passed from the cell body to the vessel wall. The gold chloride stain showed the individual cells in detail. These bipolar or ependymal spongioblasts are stained by such stains as Mallory's, which differentially stain neuroglial fibrillae; the same stain may show a collection of blepharoplasten in the cytoplasm

near the nucleus, although, according to Penfield, the importance of this point has been somewhat exaggerated. Mitotic figures were rarely found, the tumour being slower in evolution than the glioblastoma. It is named by Bailey and Cushing ependymoblastoma and is an extremely characteristic formation.

In the second type the cells were polygonal, but again showed blepharoplasten. Bailey and Cushing described seven cases, all being more organised tumours, but unfortunately not favourably situated for removal. One occurred in the cerebellar recess, three in the neighbourhood of the fourth ventricle, one arose from the septum lucidum, one in the region of the supramarginal gyrus and one in the occipital lobe. Fincher and Coon [38] studied eight cases, five of which occurred in the cerebral hemispheres.

These tumours may arise from ependyma in any situation, but also from areas where ependyma is not apparent. Small blind ependymal sacs have been shown to occur in the floor of the fourth ventricle, as well as in the central region of the spinal cord and in many other situations. The origin of these tumours from ependymal rests may be seriously considered, particularly when one observes the preponderance of such tumours in the spinal cord, where the possibility of the survival of ependymal remnants is obvious.

Kernohan, Woltman and Adson [39] found twenty-one ependymomas in fifty-one examples of intramedullary tumours of the spinal cord. They describe three definite histological pictures, all of which may be present in the one tumour:

1. In six cases canals lined by ependyma occurred. The cells were more columnar than normal, frequently showing blepharoplasten between the nucleus and the lumen.

2. In eight cases the characteristic appearance described under the term ependymoblastoma was present.

3. The third type is somewhat more controversial. It simulates the type of tumour described as neuro-epithelioma, which Penfield considers may be derived from ependyma,[40] and which Roussy and Oberling [8] class as an ependymoglioma. Seven examples occurred, the characteristic arrangement being that of rings of cells, with scanty cytoplasm and small nuclei. They were frequently arranged about cavities containing mucinous material, which had almost the appearance of thyroid acini. Other parts of these tumours were, however, characteristic ependymoma.

The Roussy-Oberling classification is somewhat similar. They accept the two types described by Bailey and Cushing but rename the polygonal cell type ependymocytome.

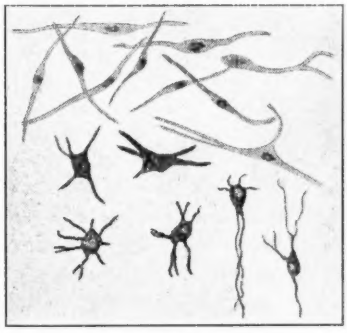
A third type is described as an ependymogliome, ependymal cells and astrocytes occurring together. A predominance of astrocytes may suggest an astrocytoma, but the presence of cavities lined by ependymal cells indicates the class to which this tumour belongs. In certain cases the astrocytes seem to be derived from the ependymal elements; in other cases the appearance suggests a proliferation of the two elements together.

The ependymomas were represented in the present series by five tumours, two of which occurred in one person. Four examples occurred in the midcerebellar region and one in the cerebrum. The cerebral example has been mentioned in discussing the anaplasia of more organised tumours. The cerebellar tumour that occurred coincidently is extremely interesting from the standpoint of histology. Macroscopically, it shows two distinct formations of about equal size, one part being a fleshy, relatively avascular, lobulated formation, and the other showing vascular channels in abundance.

The first area resolves itself into ependyma-lined lobes, surrounding a core of tissue of a definitely astrocytic and spongioblastic nature (Figs. 2 and 14). The second area is typical ependymoblastoma, the vascular channels being surrounded by well formed bipolar cells. These cells are highly protoplasmic, with extremely well marked protoplasmic processes and large vesicular nuclei. At times the processes are observed to bifurcate at some little distance from the cell body. The vascular poles pass straight to the vessel walls, or run some little way alongside them before terminating. These typical so-called ependymoblasts are brilliantly impregnated by the gold sublimate method, and show transitional forms between the simple polar shapes and undoubted astrocytes (Text-fig. 4). In those areas where the vascular channels are less evident areas occur that might well pass for simple astrocytoma. Not only are piloid astrocytes present, but also clearly marked asteroid forms with fibrillae.

A second tumour, occurring in a woman 45 years of age, was situated in the cerebellum. In structure it is irregularly lobulated, well defined and easily shelled out from the cerebellar substance (Fig. 15). The microscopic appearance is regular and reveals the typical appearance of the ependymoblastoma, as described.

A third tumour is more remarkable. What appeared to be a simple cerebellar cyst filled with a horn-like coagulated content was sectioned in that area where the wall appeared to be thickest. The structure at first sight is not unlike the appearance of thyroid acini, the vesicles being filled with a homogeneous eosinophilic substance resembling that present in the central cavity. The walls are composed of a single layer of large epithelium-like cells, varying in form from a columnar to a somewhat flattened shape (Fig. 16). This thyroid-like appearance is very evident toward the central cavity



TEXT-FIG. 4

Drawing of polar and astrocytic forms within an ependymoblastoma, showing the apparent transition between these forms.

and the impression is gained that this was formed from a coalescence of these structures. Toward the cerebellar substance the tumour is composed of numerous polygonal or cuboidal cells, arranged less regularly, but forming here and there elementary acinar structures. No mitotic figures are present, the tumour appearing relatively inactive. There is no evidence of any spongioblastic formation, the cells being apparently true ependymal cells. The picture is remarkably similar to that frequently pictured as neuro-epithelioma, but as a similar picture is described as occurring in undoubted ependymomas, no doubt is felt that the tumour is of this nature.

Summary: 1. In reviewing these tumours we find two distinct cell types present:

(*a*) The first, representing adult ependyma, retains the adult shape and forms, or forms in places cavities and clefts.

(*b*) The second type, or ependymal spongioblast, is very characteristic. A modification of its structure results in a tumour astrocyte. Whether this cell arises from adult ependyma or from a subependymal element is not apparent. It is nearer in structure to the astrocytic series than to adult ependyma.

2. Nodular areas, if opposed to the ventricular surface, whether composed of astrocytic or polar forms, may be lined by adult ependyma. This does not of necessity imply that these latter cells are neoplastic.

3. As these tumours, whether composed of ependymomatous or ependymoblastic elements, are usually fairly well defined tumours without mitotic figures, the name ependymoma, as applied to them all, is for practical purposes sufficient.

Oligodendroglioma

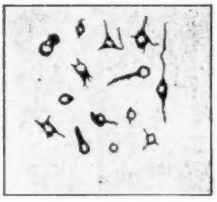
The prediction and proof that elements composed of oligodendroglia could of themselves enter into tumour formation is perhaps the crowning achievement of Bailey. For a while exact proof was wanting. Recently Bailey and Bucy [41] have clearly demonstrated the oligodendroglial nature of the cells in these tumours and their work has been amply confirmed, among others by Kwan and Alpers [42] and Roussy and Oberling.[8]

Such tumours may usually be identified by the characteristic appearance in haematoxylin and eosin sections. Masses of cells are found with small, round, hyperchromatic nuclei. The cytoplasm is poorly stained and each cell is enclosed by a rim of protoplasm with very little intervening stainable substance. They may occur singly or enclosed in groups by a denser stromal material producing a very characteristic boxed-in effect. This appearance is at times reminiscent of oligodendroglia, as seen in the stage of acute swelling. One cannot but be filled with admiration at the acumen of Bailey in deducing the nature of this tumour long before proof was obtainable.

With the Hortega silver carbonate stain, or one of its modifications, oligodendrocytes are observed. These cells are usually small and correspond to the small cortical oligodendrocyte of Robertson. The tumour is not, however, entirely composed of such cells. Many are quite unstained and may be of a much earlier form. This fact had led Penfield [11] to think that the most typical cell is in reality an oligodendroblast. Other cells are polar, while large types occur,

some of which appear to be giant oligodendroglia. Others, again, seem to be transition forms between oligodendroglia and classical neuroglia. Various transitions are described by Bailey and Bucy between oligodendroglia and frank astrocytes. The astrocytes observed by Kwan and Alpers were of a distribution that indicated many at least were inclusion forms. In the two examples encountered in this series any astrocytes observed were within the tumour edge and were undoubtedly inclusion forms, the reaction of neuroglia at the edge being very marked.

One tumour occurred in a man 22 years of age, who had presented for 5 months signs of increase of intracranial pressure. Death followed an attempt to localise the tumour by encephalography. A small nodule, about 2 cm. in diameter, was found abutting on a grossly dilated third ventricle in the region of the right foramen of Monro. Its origin was from the junction of the gyrus cinguli and the superior frontal gyrus. In haematoxylin and Van Gieson sections bands of collagenous material and small capillaries can be seen to alternate with areas of about equal width, containing a few small cells, often set in rows (Fig. 17). Their nuclei are small, round and fairly densely staining, while the cytoplasm is indefinite. The arrangement in rows suggests that of ordinary oligodendroglia and Martin [43] has described a tumour of similar appearance. In this tumour the characteristic boxed-in effect cannot be observed. Sections were impregnated by the Globus-Penfield modification of the Hortega method and by the modification recently suggested by Kwan and Alpers. In this particular tumour the former method gave the clearer impregnation. The majority of the cells are impregnated. The cytoplasm is variable in amount from a small ring of protoplasm, through uni- and bipolar forms, to well marked characteristic multipolar forms (Text-fig. 5). These bipolar forms are not interpreted as spongioblasts as they are not impregnated by the gold sublimate method and resemble the polar forms pictured by Hortega. No giant oligodendrocytes are present.



TEXT-FIG. 5

Drawing of oligodendrocytes from a similar area to that shown in Fig. 17. Penfield-Hortega stain.

A second example occurred in the left lateral ventricle of a man

26 years of age. The tumour had arisen in the roof of the anterior horn. The whole ependymal system showed innumerable small subependymal granules, the structure of which was astrocytic and the appearance not unlike that of the subependymal astrocytoma. In haematoxylin and eosin sections the main portion of the tumour shows the very characteristic boxed-in effect (Fig. 18), but other areas show the somewhat interfascicular appearance previously described in the last specimen. The blood vessels show the marked endothelial proliferation noted by Bailey and Bucy and others. With the silver carbonate stain the boxed-in areas are found to be composed of large swollen cells. The appearance is that of the typical swollen oligodendrocytes seen in the brain, thus confirming the conclusion of Kwan and Alpers that such areas represent degeneration. As, however, this appearance is rapidly assumed by oligodendroglia after death, it cannot be established that this appearance was of necessity present during life. Other areas show typical oligodendrocytes of the form previously described in Kwan and Alpers' four cases. Neither of my two examples shows calcification.

Roussy and Oberling describe two other tumour types that they consider to be composed of oligodendroglial elements. One is synonymous with the polar spongioblastomas, and the other they term a *gliome muqueuse*. This latter tumour elaborates a mucicarminophile substance of a similar nature to that observed in degenerating oligodendroglia. No examples that could be so interpreted occurred in this series.

Summary: 1. Two examples of oligodendroglioma were examined, each showing characteristic oligodendrocytes.

2. Calcification was not present in either tumour.

3. Endothelial hyperplasia was noted in the blood vessels of one tumour.

Astrocytoma

This name is applied to certain superficially dissimilar tumours, the components of which are the adult astrocyte or some modification. The astrocytes in these tumours have been noted and clearly described for many years, and Stroebe's drawing,[44] published in 1895, presents an excellent picture of the various forms encountered in the ordinary type.

Bailey and Cushing subdivided the group into a protoplasmic

astrocytoma and a fibrillary type. Neither form is entirely pure and this subdivision, owing to their similar behaviour, has been discarded for practical purposes.

At the same time it is necessary to note the various forms that the tumour astrocyte may assume. The classical type, as usually described, is that of an asteroid cell, which may or may not have developed fibrillae. Penfield, whose knowledge of neurohistology merits our greatest respect, has found this type of cell to be the exception rather than the rule. Instead he finds the common cell to be piloid, that is, to be a somewhat fusiform cell from which fine fibrillary neuroglial processes emerge, to run in parallel strands. Such a cell is analogous to the piloid astrocytes occurring in the dorsal columns of tabetics. To Penfield, the protoplasmic tumour astrocyte is a degenerate cell of the type of the *gemästete Zell*, or plump astrocyte of Nissl, and its further evolution results in the giant astrocyte. Deprivation of oxygen will produce these bizarre forms in the brain.

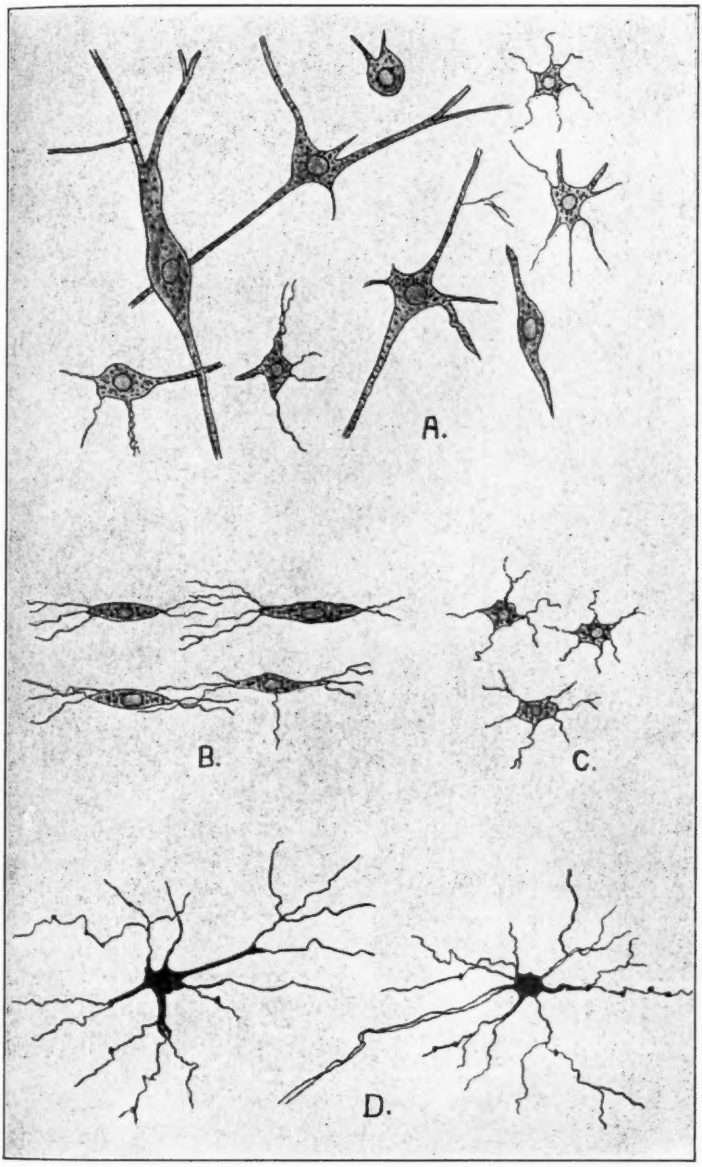
It is very difficult to be certain as to which particular influences produce the modifications of form occurring in tumour astrocytes. Such factors as the rate of subdivision of the tumour cell, oxygen starvation, and the presence of degeneration products must all modify the form assumed. The cell shape is again modified by the position in which the cell grows. In Text-figure 6B the fusiform-shaped astrocytes occurred in the region of a superior cerebellar peduncle, where their position between nervous strands determined the piloid form. Nearby in the region of the substantia gelatinosa the asteroid form was assumed (Text-fig. 6C).

Again (Text-fig. 6D), typical fibrous astrocytes were present in that part of an astrocytoma in the region of the *iter* where there was little obstruction to the full growth of the star-like expansions.

There is considerable variety also in the form assumed by the tumour. On the one hand is found a circumscribed nodule, often associated with a cyst, as in the cerebellar type so admirably described by Cushing.[16] On the other, a diffuse type occurs which may be intimately mixed with more or less normal brain tissue. This tumour, if very cellular, may be of the type of the diffuse protoplasmic astrocytoma, but if the cells are sparse and fibrilla formation is marked there may be little to distinguish it from diffuse glioses of the type of syringo-myelia, or from certain forms of cerebral sclerosis.

The so-called protoplasmic astrocytoma is composed of cells in which the protoplasmic body and its processes are very prominent, and in which few neuroglial fibrillae are present (Text-fig. 6A and Fig. 19). Tumours largely constituted of such cells may occur in both cerebellar and cerebral hemispheres. Cushing [16] has lately withdrawn many of his protoplasmic astrocytomas of the cerebrum. He notes that "many of the latter are rapidly growing tumours, with abundant mitoses, and should in all probability be separately classified. They, moreover, occur in adults with the average age of forty years." This note is significant. In the early description by Bailey and Cushing the view was expressed that the spongioblastoma multiforme might be derived from the cerebral protoplasmic astrocytoma. It is probable then that many of these latter might be better classified with the anaplastic glioblastomata. A transition of this type occurred in this series.

A man of 43 years, suffering from headache and vomiting, with mental obtundity, was found to have well marked signs of increased intracranial pressure. Owing to the presence of a motor paresis of the left side of the body, the brain was explored on the right side. A large, diffuse, inoperable tumour was found involving a considerable part of the parietal cortex. Although a small superficial biopsy portion showed many astrocytes the diagnosis of astrocytoma was not definitely made at this stage, owing to the well known astrocytic reaction that may occur at the edge of various tumours. A large cerebral hernia developed and the patient, although temporarily improved, died a few months later. At autopsy an enormous tumour was found involving the right parietofrontal area and limited on the inferior surface by the roof of the lateral ventricle. The growing edge, which was well anterior to the area adjacent to the cerebral hernia, is typical astrocytoma, and shows a multipliticy of protoplasmic forms without mitotic figures (Text-fig. 7 and Fig. 20). The deeper parts adjacent to the lines of tension induced by the protrusion of the tumour into the area of hernia are grossly cellular and present the typical appearance of the glioblastoma (Fig. 21). Mitoses, giant cells and vascular changes are in abundance. The majority of cells are typical of anaplastic glial cells and are not stained by the specific methods. Among them are irregular forms staining deeply with the gold sublimate, and without doubt of a similar nature to those occurring in the less active edge of the



TEXT-FIG. 6

Drawings of tumour astrocytes as seen in various astrocytomata.

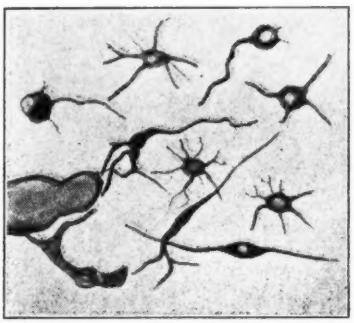
A. So-called protoplasmic astrocytes.

B, C. Asteroid and piloid forms occurring in different situations in the one tumour.

D. Fibrillary astrocytes.

tumour. It is not possible to be certain that this glioblastic transformation occurred subsequent to the change in tension induced in the tumour by the decompression operation. It is quite possible that invasion of the ventricular wall may have produced this change. At the same time no doubt could be entertained but that the central part of an astrocytoma had become more anaplastic and produced the typical picture of the glioblastoma multiforme.

Consideration of the forms of tumour cells in these so-called protoplasmic astrocytomata leaves the strong impression that the so-called astroblasts and spongioblasts result from haphazard varia-



TEXT-FIG. 7

The variation in shape of the astrocytes in a protoplasmic astrocytoma of the cerebrum.

tions in the shape of cells at a more or less similar stage of maturity. The same embryonic forms seem to the author often to represent stages of decay rather than the stages of histogenesis. The appearance often suggests that such cells divide amitotically as astrocytes, or as a more amoeba-like or undifferentiated cell.

In their atlas, Roussy and Oberling [8] describe the varying histological pictures of the astrocytomata. They are not hampered by any desire to force their tumours into a classification based on embryogenesis, but accept the subdivision into a protoplasmic and into a fibrillary group. The variations that they describe are based on morphology and are extremely instructive.

One type of fibrillary astrocytoma is the *gliome sous-épendymaire*. The characteristic cell is fusiform with processes emerging from the poles. The contained neuroglial fibrillae are very thick and their intracellular origin appears with particular clarity. Such tumours

may arise from the fusiform neuroglial elements, which reinforce the ependymal lining of the ventricular system. The small, multiple, subependymal granules, which are at times seen, present a very similar appearance. The relation of cells of this form to the polar spongioblastoma was discussed previously and a typical subependymal astrocytoma was mentioned.

The *astrocytome giganto-cellulaire* is another characteristic form and conforms to the amoeboid glioma of Lotmar.[45] The body of the cell is bulky and the shape variable (Fig. 22). The cytoplasm often shows appearances suggesting degeneration, and contains granules and lipoid droplets. The nuclei are often multiple; they may be pyknotic and peripherally placed. The processes may be long and thick, and occasionally neuroglial fibrillae are present. The likeness of these cells to ganglion cells is at times striking. Two tumours of this nature occurred in this series, each being circumscribed and well defined. One occurred in the midline of the cerebellum and the other in the frontal lobe, each being associated with a well defined cyst. In the small cerebellar nodule few neuroglial fibrillae are present, but they are numerous in certain areas of the example occurring in the frontal lobe.

Similar cells occur in the astroblastoma and Roussy and Oberling see in this a degenerate astrocytoma.

The *astrocytome pseudo-papillaire* of Crouzon and Oberling [46] presents an appearance very similar to the Bailey-Cushing ependymoblastoma. As certain of the examples develop in the neighbourhood of the ventricular system and project into it, it is possible that this type is identical. That type occurring away from the ventricular system is considered by Roussy and Oberling to consist of astrocytes set in a similar radial fashion about vascular areas, but Bailey and Bucy [37] consider the example demonstrated by Crouzon and Oberling to be an astroblastoma. The close relation of the so-called ependymoblasts and astrocytes has been discussed under the section dealing with ependymomata. The reconsideration of similar forms from a somewhat different angle in this section illustrates again the essential unity of ependyma, subependymal elements and asteroid glia.

Summary: 1. A description of the cell forms encountered in tumours of adult glial origin is given. Many of the cell shapes that have been described with names of an embryogenetic significance appear to the author to be modifications of the one adult stage.

2. Polar and piloid forms may arise in subependymal areas. They may also arise from the position of an astrocyte, which prevents the development of its processes in other than a certain plane.

3. Other factors, of which one may be anoxaemia, result in a considerable increase in the bulk of the cytoplasm. Such cells are usually known as protoplasmic astrocytes. In more advanced states of swelling the cytoplasm may be extremely bulky and show marked evidence of degeneration.

4. So-called astroblasts may occur as a result of degeneration in mature cells, by which certain of their processes may be lost, while those processes attaching them to vascular channels, and which are presumably in an area more favourable for nutrition, are unaltered, or even hypertrophied.

Pinealoma

For many years tumours arising from, or in the vicinity of, the pineal body have been described under a variety of names. Krabbe [47] was the first to recognise their real origin, and to describe them as pinealomata. Bailey and Cushing subdivided them into pineablastomata and pinealomata. The pineoblastoma, through a consensus of opinion, has now for practical purposes become merged with the medulloblastoma. The pinealoma persists as a definite type.

Some knowledge of the development of the pineal body is necessary to understand the varying histological pictures that occur in tumours of this type. This cannot be fully entered into here but is well discussed by Globus and Silbert.[48] Two types of cell are usually observed, a large cell with a clear ve icular nucleus and much cytoplasm, which may contain mitochondria, and a small cell with scanty cytoplasm and a deeply stained nucleus. The former cell is of a parenchymatous type. It appears to develop from the medullary epithelium, as do the various glial and ependymal forms, and may have some glandular function at an early stage. The small cell seems to be mesoblastic in origin, and may be transformed into ordinary connective tissue.

These facts are clear and well recognised. There is, however, a difference of opinion about certain features. Horrax and Bailey [49] believe that glioblastic elements persist in these tumours and that a spongioblastic pinealoma may occur. In addition, they have re-

cently described a pineal tumour containing typical nerve cells which they believe to be neoplastic. Schmincke [50] has also described what he believes to be a true ganglioneuroma of this region. Globus and Silbert, on the other hand, believe that such elements are not represented in the normal pineal body, and when found in a pinealoma are of the nature of inclusions.

The pinealoma presents a variety of pictures. It may show a formation corresponding to the primitive mosaic, with the large clear cells outlined by the small dark cells, or both cell types may be intimately mixed. Various degrees of transformation may also be noted between these small cells and the connective tissue stroma. If this transformation is marked the appearance of the adult pineal body is approached, with the alveolar pattern of the large cells enclosed in connective tissue stroma. In addition, multinucleated giant cells are of common occurrence. Globus and Silbert consider these to be of a foreign body nature and to be most marked in those areas where regression is occurring.

Tumours in the position of the pineal body occurred in two cases in this series. One occurred in a child. A tumour of the size of a large walnut was found lying upon and invading the quadrigeminal plate. The pineal body was not present. The tumour cell is large, with abundant cytoplasm and a large vesicular nucleus (Fig. 23). It differs markedly, however, from the usual cell of the pinealoma in that mitotic figures are extremely numerous. In addition, although the cerebellum was not invaded, the tumour was in active growth in the subarachnoid spaces between the folia. Multinucleated giant cells are frequent and are undoubtedly of neoplastic origin. The nuclei are at times peripherally placed. Usually the cell centre is, however, crowded with a knot of nuclear forms or is occupied by an enormous, poorly stained nuclear mass. Although such forms indicate insufficient nutrition they are not confined to the more degenerate areas. They are, however, larger and more abundant in regions where the wide spacing of the cell units suggests an oedematous condition. None of the typical small cells is observed. Blood vessels are extremely numerous but thin-walled.

Hypertrophic astrocytes are present at the invaded margin, but are absent from the tumour proper. In the same way degenerating nerve cells and their processes are present in that part of the tumour which has invaded the quadrigeminal plate, but in no other portion.

Connective tissue strands are present throughout either in prominent strands or more intimately mixed with the tumour cells.

In the other example the tumour was grossly necrotic and no definite histological picture could be obtained.

Summary: 1. In one example of pinealoma only the large parenchymal cells were present.

2. The tumour was unusual in that it was highly malignant and invading the subarachnoid space.

3. No astrocytic or neuronic forms were observed within the true tumour zone, although present at the edge.

Ganglioneuroma

Tumours composed of nervous elements present considerable difficulty. They fall into two main groups, one composed in the main of adult nerve cells, and the other of forms that suggest neuroblasts. The former are among the rarest of tumours, none occurring in the Bailey-Cushing series, but the latter exist in considerable numbers.

Well differentiated cells may be identified by the nucleus with a prominent nucleolus, and by the presence of Nissl bodies and neurofibrils in the cytoplasm and in the processes. This having been done, it must be proved that these are true tumour cells and not preserved nerve cells within a tumour resulting from invasion of a heterotopic or of a normal nuclear mass. There must be such evidence of division of nerve cells as binucleated forms, or proof that the adult forms are derived from subdividing, less differentiated forms. If these criteria are accepted the number of well differentiated ganglioneuromata occurring within the cerebrum will be exceedingly small. The cerebellar type differs somewhat from the cerebral type, being much more diffuse, and has been well described by Bielschowsky and Simons.[51]

A considerable number of examples of ganglioneuromata, or gangliomata, have been reported in which the cells are not so evidently true ganglion cells (Fig. 24). Courville has made an extensive survey of the entire group and has summarised the majority of examples of both types. Other examples have since been reported.[52, 53, 54] It is probably better at present to preserve an open mind concerning the true nature of many of these tumours. Tumour astrocytes may be exceedingly bewildering, not only in their general

shape but in the appearance of the nucleus. One may take individual cells from their surroundings and be quite unable to say on morphological grounds whether such a cell is a neuroblast or an astrocyte. True neurofibrils and Nissl bodies are usually absent from these cells, and the appearance of the nucleus may be extremely deceptive. Cells showing a nucleus with a large central nucleolus must not be considered as neuroblastic, unless there is undoubted evidence of the presence of neurofibrils and Nissl bodies (Figs. 25, 26, 27). Many of the large protoplasmic tumour astrocytes may also be impregnated with certain of the silver stains; and, if the cytoplasm contain granular degeneration products, they may suggest by their appearance the presence of Nissl bodies.

PART II

The Preservation of Neuronic Elements

It is frequently difficult in any neoplasm to be sure as to which is tumour cell and which the cell derived from the invaded tissue. The stroma is a reactive structure, which, although it supports the vascular supply of the tumour tissue, often presents an appearance that suggests an attempt to confine and isolate the neoplasm. This particular reaction in ordinary body tissues is a reaction of the supporting and vascular tissues and is exhibited by elements of mesoblastic origin. Thus, when a mesoblastic tumour invades a tissue of the same origin it may be difficult to say whether a particular cell is neoplastic or not.

At the same time certain elements invaded by a tumour, even if highly specialised in function and of non-mesoblastic origin, may show a singular degree of resistance. Thus the small bile ducts may remain isolated in a carcinoma invading the liver, or a peripheral nerve may survive in the midst of a carcinoma nodule. Even fine, non-medullated nerves may persist in ordinary body carcinoma and attempts have been made to prove that the appearances of these represent regeneration and innervation of the tumour mass.[55]

It is often a very striking feature of the silver stains, as applied to glial tumours, that numerous nerve fibres seem to pass through the neoplasm, and present no great evidence of degeneration. The small degree of loss of function in comparison with the actual zone of invasion is certainly related to the survival of these elements. The

incidence of sudden vascular changes, however, produces an immediate interruption of function and is responsible for much of the symptomatology of infiltrative tumours, which may amaze the pathologist by their size.

Not only may nerve fibres be observed deep within these neoplasms, but at times, and in particular in the vicinity of vessels, the arrangement of non-medullated fibres may suggest actual regeneration.

Cajal,[56] in his classical work, has reviewed the subject of neural regeneration within the central nervous system. By numerous experiments he has shown that regeneration is attempted, but is grossly inefficient. It is usually confined to neurofibrillar activity within the proximal part of an injured axone, and in occasional feeble and abortive sprouts. The experiments of Tello [57] suggest that this poverty of response is not so much the property of these particular neurones, as the absence of some substance with a neurotropic effect. He has grafted within the cerebrum segments of degenerating peripheral nerve containing bundles of multiplying neurilemmal cells. An abundant outgrowth of neurofibrillae was produced from neighbouring divided nerve tracts in the direction of the graft. It is presumed that it is the absence of true neurilemma or some kindred element within the central nervous system that determines the poverty of regeneration.

Bielschowsky [58] in 1906 found at the margin of and within gliomata appearances that were identical with the phenomena of regeneration, as observed within peripheral nerves. These took the form of fine non-medullated nerve fibres, at times arranged in perivascular plexuses. The axones followed atypical paths and frequently terminated in *cônes de croissance*, in rings, or in more complicated fenestrated structures, all of which may be observed in regeneration. Herxheimer and Gierlich,[59] and Miyake,[60] separately observed similar appearances at a later date, but concluded that the fibres represented the remnants of preëxistent nerve fibres, rather than regeneration. Cajal, however, accepts certain evidence as showing the possibility of regeneration.

Thus senile plaques have been observed by Fischer [61] to show undoubted evidence of penetration by neurofibrillae. Newly formed dendrites have been noted in the pyramidal cells in tuberose sclerosis (Bielschowsky and Gallus [62]), and in the pyramidal cells in

Ammon's horn in senile dogs (Lafora [63]). Spatz,[64] too, has noted similar appearances in the so-called myelin spots.

It may be said then that the occurrence of newly formed neurofibrillae is not an impossibility in the presence of some unknown neurotropic substance, which may be present in degenerating areas. In a severe injury to an axone in the central nervous system, however, the distal part completely degenerates. The proximal part forms a retraction ball, as shown by Cajal, with at times some feeble attempts at regeneration. Finally the area atrophies to the level of the nearest collateral, which usually hypertrophies.

The nerve cell, if severely injured, rarely recovers, the evidence for the subdivision of nerve cells within the central nervous system being extremely scanty. Many so-called appearances of subdivision have been subdividing neuroglial cells, although binucleated pyramidal cells have occasionally been observed.

The presence of nerve fibres within the gliomata, although denied by Virchow, has been known since the end of the last century. The Weigert stain for the medullary sheaths does not show the true extent of their penetration. Many of the nerve fibres, on entering certain of the gliomata, may lose their myelin sheath and persist as naked axones. These latter can be satisfactorily demonstrated only by the silver methods.

The presence of nerve fibres was noted in varying amounts in the majority of the various gliomata examined in this series. In the astrocytomata they were fairly constantly present.

The photograph (Fig. 28) is from an area of a diffuse astrocytoma well within the edge. As the tumour extended from the vertex to the middle of the left frontal lobe and was of a slowly growing type, it is obvious that it must have been present for many years. The first ascertainable symptoms occurred only 6 months before death, which followed operation. They then were due to a general increase in intracranial pressure rather than to any focal lesion. This gives us undoubted proof that the enclosed neurones were not notably diseased, but in fair physiological health. It is probable that the absence of marked haemorrhagic or necrotic changes within tumours of this type explains the preservation of the nerve elements. The neoplastic astrocytes are not of themselves markedly destructive of the neurones, which are readily preserved until too gross a gliosis occurs. They may then degenerate owing to the effects of pressure,

or owing to the necrotic changes engendered by interference with their blood supply.

The glioblastoma differs considerably from the astrocytoma. Haemorrhage, thrombosis and degeneration produce marked hiatuses in the invaded network of axones and their collaterals. The result is that it is in the neighbourhood of the vessels that the persisting nerve fibres are mostly found. Appearances suggesting a perivascular plexus are often very striking and one of the original examples described by Bielschowsky,[58] judging by the illustrations, was undoubtedly an example of the glioblastoma multiforme.

These so-called plexuses probably occur owing to the ingrowth of new vessels through a network of nerve fibres; their early appearance may be observed in the areas that are becoming vascularised beyond the tumour edge.

In non-degenerative areas of the glioblastoma a persisting network of naked nerve fibres is not infrequent. The impression is formed that it is less the neoplastic cell than the effects of degeneration and haemorrhage that produce the damage to these elements. Secondary carcinoma forms a strong contrast in this regard. Although a certain number of axones may persist and even present appearances similar to those described by Oertel [55] in the innervation of tumours elsewhere, they mostly degenerate speedily.

In one example of glioblastoma the persistence of neuronic elements is notable. This tumour is less degenerative than is usual, but is highly cellular. It is composed of undifferentiated cells set in a syncytium-like arrangement, but showing the typical vascular hyperplasia. It extends from the temporal lobe through the thalamus and hypothalmic regions into the upper part of the pons, and has involved much grey matter. Considering its extent, the paucity of symptoms was extraordinary. In all areas preserved nerve cells with their processes are abundant (Fig. 29). So marked is this feature that sections of certain areas superficially resemble those of the adult ganglioneuroma. The nerve cells are not entirely healthy, but present evidence of degeneration and marked alteration of the neurofibrillar content, although these appearances may be the result of postmortem changes.

Figures 30 and 31 are from a tumour removed at operation from a child's cerebellum. On account of a tangle of nerve fibres and cells, in conjunction with undifferentiated elements, it had been classified

as the rare adult ganglioneuroma. There does not seem to be any evidence of intermediate forms between the two types, and in addition the nerve cells seem to be mostly degenerative. It is considered, therefore, that such cells are inclusion forms, or represent a heterotopic rather than a tumour formation.

It is usual to find nerve fibres, and even occasional nerve cells, within the medulloblastomas. In one example the penetration of unaltered axones is marked (Fig. 32). Another extremely malignant example shows persisting nerve cells well within its substance, which are apparently derived from a strand of almost unaltered nerve tissue in the vicinity (Fig. 33). In Figure 52 of the Bailey-Cushing monograph, a multipolar neuroblast is pictured in the substance of a medulloblastoma. This appearance is strikingly reminiscent of a nerve cell inclusion, as are also the neuroblasts shown in Figures 50 and 51. Cajal noted that in animal experimentation degenerating nerve cells of the smaller type may assume the appearance of neuroblasts. It must be shown clearly that an area said to contain neuroblasts has not involved any nuclear mass. Even so, the question of the identification of neuroblasts is difficult, as has already been pointed out.

Cajal has also pointed out the phenomenon of preserved nerve fibres. In experimental lesions neurones may be preserved from the effects of autolysis by exudate and, although dead, present the appearances of exquisite normality with a clear, fine definition of nucleus and neurofibrils. Thus an instantaneous death may produce the appearance of unaltered, live neurones, an appearance that has also been noted by Marinesco [65] in vascular lesions.

In the tumours examined no appearances were noted that would offer unequivocal proof of regenerative attempts on the part of the neurones. Fine networks may be noted about blood vessels, but *cônes de croissance* and similar appearances are rare. Occasionally a somewhat fenestrated net is observed, but it is extremely easy to read into such appearances deductions that are not correct.

Summary: 1. Intact neurones are frequent in the gliomata, particularly in the more slowly growing, non-degenerating types.

2. In the degenerating parts of rapidly growing tumours naked nerve fibrils may persist about vascular channels. Networks and plexuses were observed, but did not present appearances suggesting regeneration.

3. Included nerve cells may mimic neuroblasts. The difficulties in distinguishing neuroblasts from other neoplastic cells are discussed.

The Mesoblastic Content

The reaction of the fibroblastic and vascular structures will not be considered. It has been amply described by many authors. The differentiation of mesoblastic derivatives from glial tissue usually presents little difficulty, although certain authors have described a transition between the two.[66] The reaction of the cellular lining of the Virchow-Robin space has also been described, and is according to Bailey and Bucy of some importance in the astroblastomata.

Microglia has formed the subject of many papers. Penfield[67] has admirably described its reaction about the gliomata and shown all stages of the transition between it and the compound granular corpuscles.

The Occurrence of Oligodendroglia

Oligodendroglia, although of the same origin as neuroglia, will be discussed only shortly here. Owing to its fragility it is not usually well stained about tumours in postmortem material. According to Roussy, Lhermitte and Oberling,[68] and lately Cramer and Alpers,[69] it too may give origin to compound granular corpuscles.

At the same time perineural satellitosis has been observed by Bailey and Bucy about the oligodendrogliomata.[41] Otherwise its activities appear to be inconspicuous.

The Preservation of Classical Neuroglia and its Reaction Forms

A full understanding of the reaction of ordinary classical neuroglia, fibrous and protoplasmic, is of great importance if the histology of the gliomata is to be fully comprehended.

The glioma is a neoplasm of glial origin, invading glia. As classical neuroglia is a labile tissue analogous to ordinary connective tissue, it is only to be expected that it should react to an irritant or foreign body as does connective tissue. This is indeed so in the brain, but the reaction of neuroglia is slow as compared with its analogue in ordinary body tissues. Even so, it may very effectively encapsule an irritant body, provided that body is not too noxious and gives it the necessary time for proliferation and the production of fibrils.

The neuroglia of the grey matter is known as protoplasmic neuroglia. This differs from the fibrous neuroglia in the white matter in having a higher cytoplasmic content, branching protoplasmic processes, and a structure free from fibrils. Protoplasmic neuroglia may, however, produce fibrils and become typical fibrous neuroglia. As the white matter is approached from the grey, transition forms appear. Both types show the usual thick processes of attachment to neighbouring vessels.

The older methods of staining, such as those of Weigert, although showing the fibrils well, did not demonstrate clearly their relation to the cell cytoplasm. They were considered then to be structures independent of the cell body. The modern methods of staining, as the Cajal gold sublimate and the Hortega silver methods, have emphasised their close relation to the cell. It is now held in many quarters that glial fibrils are always continuous with the glial cell, and have in fact a narrow protoplasmic sheath. It would, however, be difficult to believe that they are dependent for their perpetuity on the cell, as in a dense gliosis cells may hardly be evident. It is probable that the fibrils may survive even when the cell is defunct.

It is widely recognised that in the presence of cerebral neoplasms glial cells may hypertrophy and proliferate, resulting in an increased number of large glial forms. This reaction is dependent on the nature of the irritant. A rapidly growing neoplasm, provided it is not too rapid and too noxious, will produce many hypertrophic forms, while a slowly growing type may produce few. However, even in these examples, although actual cells may be scanty, there may be a marked increase in the glial fibrils at the border of the tumour. Thus a slowly forming cyst, or a compressing meningioma, may produce a dense reactive gliosis. A similar gliosis may occur subsequent to the degeneration of nerve cells and tracts, whether the process be inflammatory, toxic, or simply abiotrophic.

Apart from this gliosis, increased numbers of neuroglial cells and hypertrophic forms have for many years been noted at the margins of tumours. They occur at the invading margins of certain secondary carcinomata, sarcomata, and even about the transplanted sarcomata of rodents, as well as about the gliomata.

The study of the margins of secondary carcinomata in the brain forms an excellent comparative study, for here there can be no question as to which is glial reactive cell and which is neoplastic. In some

examples there is a marked glial reaction, in others the zone of degenerative material about the tumour is so great that these glial forms are hardly evident.

The study of one small nodule of adenocarcinoma proved instructive. It is 5 mm. in breadth and so situated in the cerebral cortex as to be half within the grey matter and half within the white. About that area which borders on the grey matter, a dense but narrow zone of enormously hypertrophied protoplasmic astrocytes occurs. In the area adjacent to the white matter there is no reaction, and the astrocytic band ceases accurately on each side at the junction of grey and white matter.

Other examples of secondary carcinoma so far studied serve to show, although less dramatically, that the grey matter is more productive of these reaction forms than the white. Away from the margin of the neoplasm fairly normal protoplasmic astrocytes may be seen amidst degenerating nerve cells. By a fairly rapid transition these forms have become huge at the tumour margin. The cell body and thick processes are densely stained with the gold sublimate. Their vascular attachments are prominent, heavy and often multiple. Not only do the long processes pass to the vessels, but into the interstices of the adenomatous nodules, and occasionally a process may appear to be attached to the neoplastic wall. Compressed astrocytes may at times seem to be contained within the interstitial tumour tissue, but this is unusual. It is interesting to speculate on the capacity for alteration in position these protoplasmic astrocytes may possess. Roussy considers, contrary to general opinion, that classical neuroglia of both types may produce the amoeboid and phagocytic compound granular corpuscles.

Cajal [57] believes in the migratory capacity of astrocytes. In experimental wounds he finds that if a small vessel be coagulated, the sucker foot and vascular processes of an attached astrocyte will become poorly stained and even undergo granular disintegration preparatory to migration. In other necrotic or thrombotic areas he has observed a migratory flight of astrocytes away from the presumed noxious or poorly oxygenated area. "The pedicles of the neuroglial cells all orientate themselves in a direction opposite to the loss of substance. These appendices are parallel and two to three times their normal length." They are stretched out in the direction of the line of flight and the appearance in their figure is strongly reminis-

cent of the streamers of astrocytic processes coming from between the masses of the advancing adenocarcinoma. He regards neuroglia as having this amoeboid capacity of losing the unsuitable attachment, of migrating and finding fresh vascular attachments elsewhere. Certainly the appearance at the edge of carcinoma nodules, particularly if their small alveolar structure is preserved, might suggest this, by the heaping up of the hypertrophied astrocytic forms and the passage of long thick processes in parallel between the nodules of the advancing neoplasm.

As noted, the white matter is much less prodigal of its astrocytic forms. Hypertrophic types, however, occur and may be fairly prominent. Possibly owing to the fact that they are placed between parallel nerve tracts they are not so apt to assume the asteroid but more a piloid form, which is particularly readily seen if the section is cut in the direction of the longitudinal tracts.

At times the glial proliferation about secondary carcinoma assumes such proportions as to become a problem of practical importance. Carmichael [18] has noted about a carcinoma nodule a gliosis that was so marked as to resemble the appearance of astrocytoma. As the nodule required some little search to find it is apparent that again we have a demonstration of the pitfalls awaiting those who deduce too much from the examination of small pieces of tissue alone. Certain of Cushing's [16] earlier reported cerebellar astrocytomata have proved, with further study, to be a reactive gliosis about non-glial tumours. The angioblastomata in particular were confused by this deceptive gliosis.

Such a study affords a basis of contrast and comparison for the study of similar reaction forms at the margins of gliomas. The more rapidly spreading types are frequently productive of much astrocytic proliferation; the more slowly growing types as a rule produce less, although there may be much fibrillar gliosis.

One considerable difference, however, between these tumours and the carcinoma group is observed. In the latter form any contained neuroglial forms are speedily destroyed. In the gliomata they may find an environment somewhat of their own kind, and may not only remain embedded in the mass, but proliferate and produce many unusual forms. The great enemy of these glial cells is less the tumour cell than the effects of vascular thrombosis, haemorrhage and cell necrosis. If the tumour is not of the degenerative type such forms

may persist in quantity, varying from fairly normal forms in some of the slowly growing tumours to hypertrophic forms occurring in those tumours where a hypertrophic reaction is found at the edge.

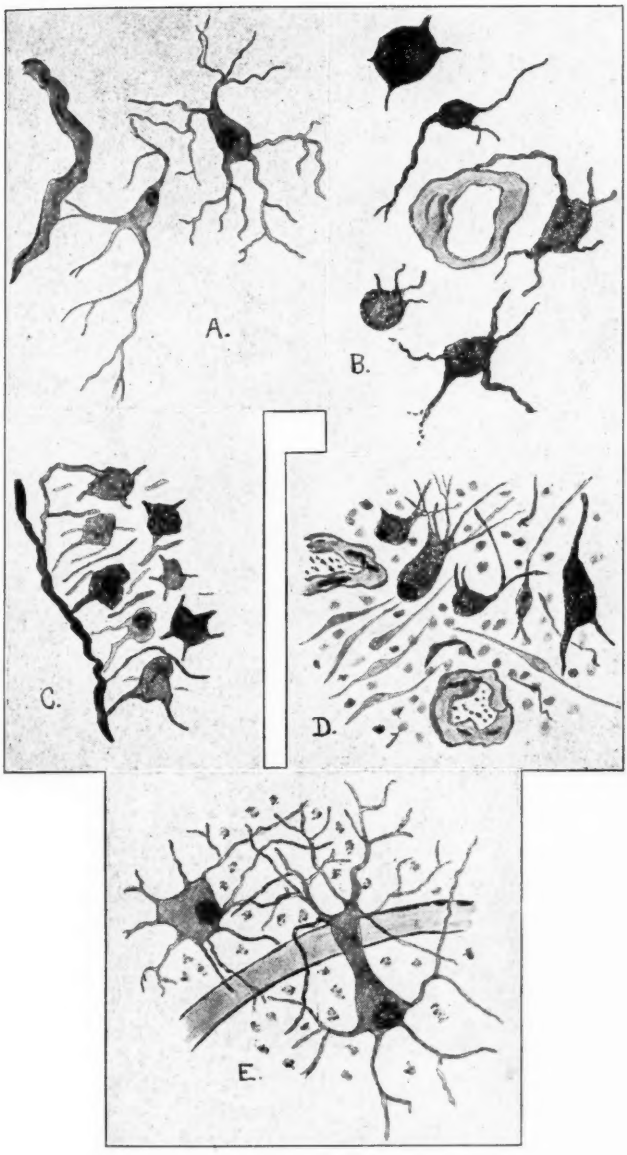
The study of the spongioblastomata is of great interest in this respect. Each tumour is different in certain respects, but certain fairly broad types of reaction may be observed. It must be noted that the adjacent grey matter seems productive of larger and more hypertrophic forms than the white. Hence the appearance at different parts of the edge of a single tumour may be variable.

Four general types of reaction were noted:

1. Although hypertrophic amoeba-like forms occur away from the tumour edge they rapidly become degenerate, poorly stained, and disappear. In this type of glioblastoma no inclusion forms are observed. Such an appearance may be noted at the edges of certain carcinoma nodules. It is presumed that in this type noxious products determine the death and disappearance of the astrocytes.

2. A transition between these hypertrophic forms and certain astrocytes found within the tumour forms a very definite feature. This was clearly seen in a tumour of one temporal lobe which was interpreted as an anaplastic ependymoma. The illustrations (Text-fig. 8) show a zone of deeply staining cells at the tumour edge. At the margin many of these cells are of amoeboid appearance, with short stubby processes, and the appearance is strongly suggestive in places of an area of so-called astroblasts (Text-fig. 8c). Within the tumour these same forms occur, but with many polar cells of the nature of ependymal spongioblasts and numerous unstained, undifferentiated forms. If the tumour edge had not been stained it could have been easily assumed that a spongioblastic tumour was differentiating into astrocytic forms. Another area of the tumour (Text-fig. 8E) presents an appearance less difficult of interpretation. Here we have well formed astrocytes associated with undifferentiated cells, without any suggestive transition forms.

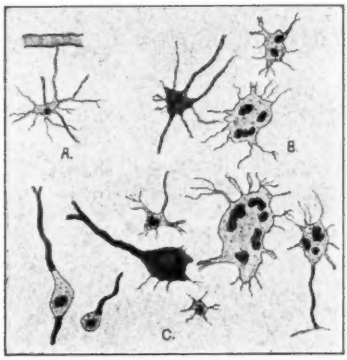
It must be noted that spindle and asteroid forms may occur together as neoplastic cells, and presumably divide at separate levels of differentiation. Cairns and Russell [14] describe a spinal metastasis from a glioma in which both forms were indubitably neoplastic. Although they describe their tumour as a glioblastoma, they are not at all sure that it may not be an anaplastic astrocytoma. It must also be noted that similar cells may occur together in an ependymoma.



TEXT-FIG. 8

A. Astrocytes showing hypertrophy away from the tumour edge. B. Nearer the edge, showing deeply staining forms, and the loss of the fine ramifications. C. The amoeboid zone at the tumour edge, mimicking astroblasts. D. Within the neoplasm. Undifferentiated cells, with ependymal spongioblasts and large astrocytic forms of the inclusion type. E. A part of the tumour, an anaplastic ependymoma, far removed from the above. Only undifferentiated forms were present here with the large astrocytes.

3. In one tumour multinucleated giant cells are prominent. In ordinary haematoxylin and eosin sections these cells present all the appearances of foreign body giant cells (Fig. 34). In a deep section of the tumour edge stained by the gold sublimate method their origin from neuroglia is apparent (Fig. 35). As the edge is approached from the normal brain, ordinary fibrous neuroglia gives place to hypertrophied and often multinucleated forms. Deep within the tumour these forms are very evident, particularly in the vicinity of



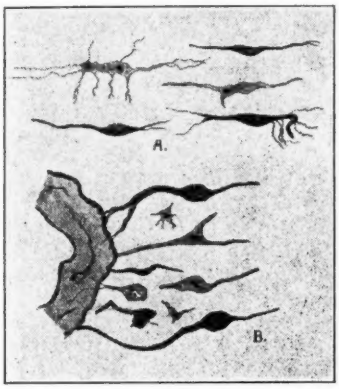
TEXT-FIG. 9

A drawing demonstrating the transition between tissue astrocytes, and giant astrocytes within a glioblastoma multiforme. A. An astrocyte just outside the zone of hypertrophy. B. Multinucleated astrocytes outside the tumour edge. C. Astrocytes of the inclusion type within the tumour.

vessels. Some of the cells are of enormous size, with the nuclei arranged at the periphery of the cell; other cells are small, almost of the size of the normal astrocyte; others again are of bizarre shape — club-shaped, flask-like, or polar (Figs. 36, 37, and Text-fig. 9). The tumour cells are undifferentiated and there do not seem to be any intermediate types between these and the deeply staining inclusion cells. In one part of the tumour there is a definite capsule of giant astrocytes. Their large fibres are mixed in a dense network. This area is cortical and corresponds to the wall of a degeneration cyst. A portion of the tumour wall taken in this vicinity would have conveyed the impression that an astrocytoma was being dealt with, but

a comparison of this with other areas leaves no doubt that these cells were not neoplastic but reactive.

Although giant cells in a glial tumour may be and usually are neoplastic, in this particular example they are of the inclusion type. Considerable doubt is expressed by many writers as to the origin of the giant cells in the gliomata. They are considered by some to be true neoplastic cells, and by others to be included cells. Giant cells are usually neoplastic in origin, but many of the astrocytic and



TEXT-FIG. 10

A. Drawing of astrocytes outside the tumour edge of an undifferentiated glioblastoma. The piloid shape is assumed owing to the compression of a band of parallel nerve fibres. B. The same forms passing into the tumour as a perivascular cuff.

modified astrocytic forms encountered in the present series were undoubtedly derived from large reactive forms at the tumour edge.

4. The next example, the glioblastoma, presents a somewhat different appearance, the astrocytic forms being more confined to the larger vessels within the tumour (Figs. 8, 38, and Text-fig. 10). At the edge of this tumour are seen many forms, mainly piloid in character. The size of the processes is extremely variable and may be dense and highly stained, or fine and hair-like. The one cell may show both types of processes. Binucleated cells are present, and Text-figure 10A shows a cell with a constriction showing it to be

about to divide. The tumour substance contains closely packed undifferentiated cells and prominent vascular cuffs of an astrocytic nature. Not only is the appearance of these cells similar to that occurring in the reactive zone, but occasionally a vessel may be seen entering the tumour surface, surrounded by the same cuff, in continuity with the outer zone of astrocytes. The form of these perivascular cells reveals types that may be described as astroblastic, asteroid, or even spongioblastic. Yet they are derived from brain astrocytes and cannot be given an embryonal value.

The astrocytes observed within the medulloblastomata have usually been described as resulting from the process of differentiation. An area is shown in Figure 39. This method of derivation is inconceivable in this tumour. There are no suggestions of any intermediate forms, and no other deduction can be made but that they are non-neoplastic cells. In another example, where the tumour edge is clearly defined, their passage into the tumour can be traced. It is felt that it is insufficiently recognised that tissue astrocytes associated with the vascular system may form a stroma within these tumours. Further, in the one example of dissemination of a medulloblastoma within the subarachnoid space occurring in this series, no astrocytes can be observed in these tumours growing in a non-glial tissue.

The astrocytoma presents a more difficult problem. The astrocytic reaction at the edge of many of these slowly growing tumours is not marked. At times, however, for no very apparent reason, it may be. Thus, in one cerebral astrocytoma, although diffuse in type, a well marked edge can be noted in one place at the margin of the grey matter. An increase in number and size of the normal astrocytes can be traced from without to the tumour edge. After that, in the tangle of forms, it is impossible to say which is tumour cell and which true astrocyte.

The current views on tumour formation do not foster the belief that the cells of invaded tissue may become neoplastic. We have then the possibility in an astrocytoma of a mixture of neoplastic and non-neoplastic astrocytes. Astrocytic cells at a tumour edge may, moreover, assume somewhat the form of tumour cells. Lhermitte and Oberling have noted the curious branching shape and volume of the astrocytes at the margin of tumours of the nature of the *astrocytome giganto-cellulaire*. It is possible that the same chemi-

cophysical factors may have caused uniform swelling in the cytoplasm of invading and invaded cells alike. This was extremely well shown in one example in this series.

The oligodendrogliomata frequently show many astrocytic forms and an interpretation of transition between these and oligodendroglia is frequently suggested. Kwan and Alpers expressed doubt in certain of their cases as such forms were more numerous near the margins of the tumours and near the vessels. In the one example in this series in which astrocytic forms occurred within the tumour there was no doubt that they were inclusion types. A well marked astrocytic reaction occurred at the margin, and was continued for a limited distance within the tumour. Moreover, no transition forms were apparent. This observation is merely recorded, and no attempt is made to deny that such transition forms do occur. The relation of oligodendroglia and astrocyte is too close to doubt that such a transition is not only possible but highly probable. It is, however, not a necessary assumption in every case.

Summary: 1. To the already varied picture of the glioblastoma multiforme further variations may be added by included astrocytes. Such cells may vary from the small astrocytic forms to huge multinucleated giant cells. In addition they may assume a polar form, or may present the appearance of astroblasts.

2. Such cells are particularly apt to be present near the edges of tumours and in the vicinity of vessels, although they are not confined to these areas.

3. The protoplasmic astrocytes of the grey matter are particularly apt to give origin to these larger forms.

4. It is possible that many of the variations in form of the brain astrocyte may be produced by such physicochemical factors as anoxaemia, degeneration products, the direction of stress, or the texture of the tissue.

5. Appearances may be present that suggest astrocytes may divide or attempt to divide within the tumour substance. They form there a type of stroma in the less degenerative areas.

6. In certain of the medulloblastomata an astrocytic stroma may be present. Such a stroma in the examples examined was certainly non-neoplastic.

7. Evidence is adduced that suggests certain of the astrocytomas may contain non-neoplastic mixed with the neoplastic astrocytes.

8. A similar stroma may occur in any of the gliomatous tumours in those areas in which degeneration is not prominent.

9. Many of these non-neoplastic astrocytes are introduced along with the blood vessels supplying the tumour. Occasionally they may form an actual cuff about such vessels.

Conclusions

One conclusion derived from this study is that names with an embryogenetic significance do not in all cases give the true values of the cells described. This in particular applies to the medulloblast and to certain of the spongioblasts and astroblasts. The neuroblast is also a cell that is particularly difficult to identify. It may be confused with included nerve cells, cells of the astroblast type, and even with certain anaplastic, rapidly subdividing cells.

The nature of a tumour will frequently be more correctly interpreted by the assumption of anaplastic changes overtaking a well differentiated tissue rather than ascribing it to differentiation of embryonal cells.

The medulloblastoma of childhood, however, possesses certain qualities that suggest the possibility of an embryonal origin.

The ordinary gliomata appear to fall into certain categories, as follows:

1. Tumours of adult tissue:
   (*a*) Astrocytoma and its modifications.
   (*b*) Ependymoma and its modifications.
   (*c*) Oligodendroglioma.
   (*d*) Pinealoma.
   (*e*) Adult ganglioneuroma.
2. Highly anaplastic tumours which may occur independently or in association with any of the above (glioblastoma multiforme).
3. Transitional forms between the above:
   (*a*) Astroblastoma.
   (*b*) Polar spongioblastoma.
4. The medulloblastoma (possibly a true embryonal tumour).
5. Rare tumours of the type of medullo-epithelioma and neuroepithelioma, concerning which no opinion is expressed here.

The mitotic figure content of such tumours offers the most ac-

curate index of their activity, rather than deductions derived from their resemblance to embryonal cells.

The difficulty in distinguishing between truly neoplastic cells and those that are derived from the glial tissue is discussed in some detail. The great advantage of postmortem material as opposed to operative fragments is here apparent.

I am indebted to Professor P. MacCallum, to Dr. W. J. Penfold and Dr. R. A. Willis for many helpful suggestions and much valuable criticism. To Dr. Willis I am indebted in addition not only for constant assistance and advice, but for all the photomicrographs produced in this article, as well as for the preservation of many valuable specimens.

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DESCRIPTION OF PLATES

PLATE 137

FIG. 1. Section of a small, well defined tumour growing on the floor of the third ventricle. The convoluted bands of columnar cells suggest the medulloepithelioma, yet the tumour showed little evidence of activity. Haematoxylin-eosin. × 350.

FIG. 2. An ependyma-lined cleft in a cerebellar ependymoma. Haematoxylin-eosin. × 480.

FIG. 3. So-called medulloblasts in a cerebellar medulloblastoma. Haematoxylin-eosin. × 750.

FIG. 4. Polar forms of a medulloblastoma occurring in a child's cerebrum. One cell is in mitosis. Haematoxylin-eosin. × 750.

FIG. 5. A frontal lobe tumour composed almost entirely of giant cells. Certain of the nuclei contain a single nucleolar-like mass, giving the cell somewhat the appearance of neuroblasts. The tumour contains numerous mitotic figures. Haematoxylin-eosin. × 450.

FIG. 6. Astroblasts in a glioblastoma multiform. Pyridine silver. × 750.

FIG. 7. Small unipolar cells (see Text-fig. 2c). Gold sublimate. × 750.

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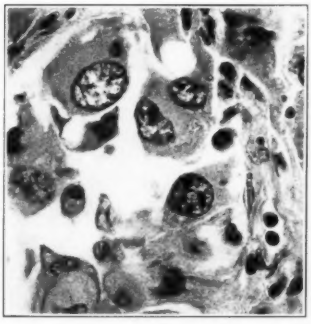

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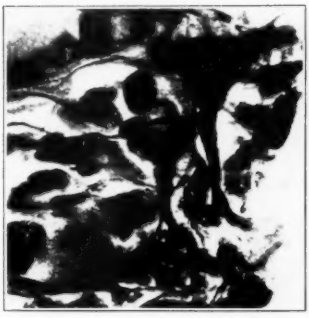

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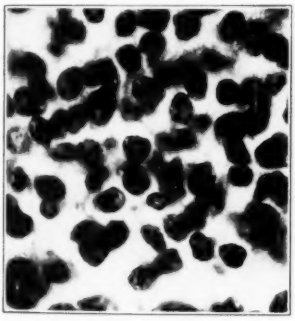

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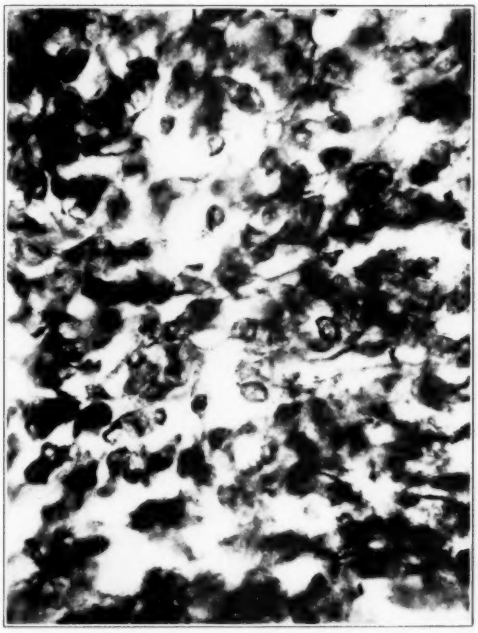

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Cox

Cytology of Glioma Group

PLATE 138

FIG. 8. An astrocytic cuff within a glioblastoma multiforme. This is derived from the hypertrophied astrocytes of the tumour edge. Gold sublimate. × 60.

FIG. 9. Bipolar cells in a glioblastoma multiforme. Iron haematoxylin. × 400.

FIG. 10. An astroblastoma. The cells are enclosed by connective tissue bands, to which their processes are attached.

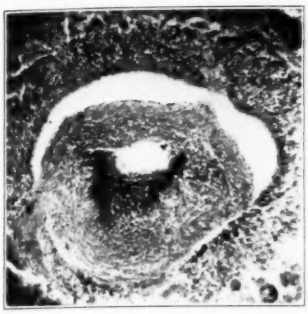
FIG. 11. Individual cells of Fig. 10. Gold sublimate. × 450.

FIG. 12. Polar cells in a pontine tumour in a child of 4 years. Iron haematoxylin. × 480.

FIG. 13. A glioma of subependymal type. Haematoxylin-eosin. × 450.

FIG. 14. A deeper part of the same tumour, showing ependymal cells. Many of these were shown by the gold sublimate stain to be astrocytic. Haematoxylin-eosin. × 480.

FIG. 15. Arrangement of ependymal spongioblasts about vascular channels. Silver pyridine. × 90.



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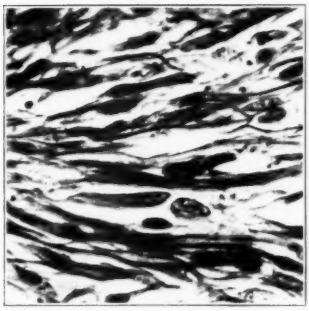

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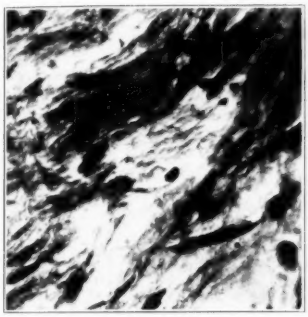

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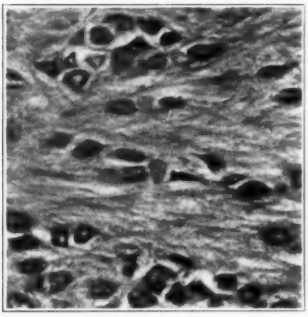

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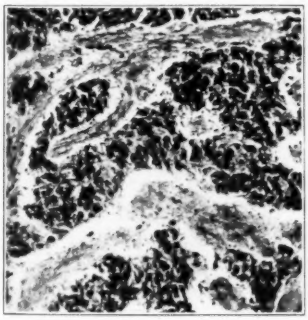

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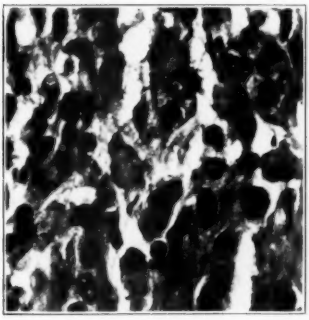

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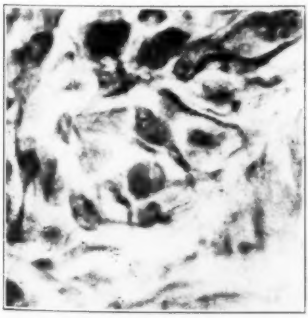

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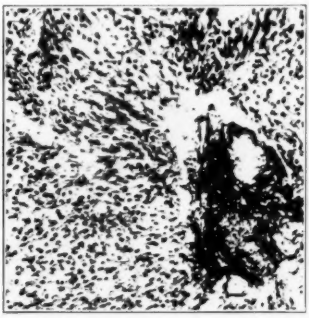

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PLATE 139

FIG. 16. Ependymoma of neuro-epitheliomatous type associated with a cerebellar cyst. Haematoxylin-eosin. × 150.

FIG. 17. Oligodendroglioma, showing the interfascicular arrangement of the cells. Haematoxylin-eosin. × 450.

FIG. 18. Swollen oligodendroglial cells in an oligodendroglioma, producing the boxed-in effect. The vascular endothelium is prominent. Haematoxylin-eosin. × 300.

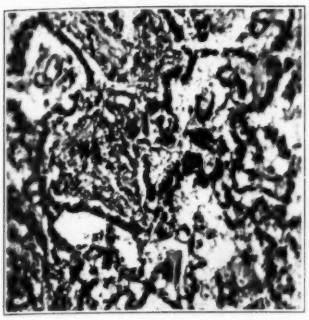
FIG. 19. Protoplasmic astrocytes. Gold sublimate. × 750.

FIG. 20. A cerebral astrocytoma. Gold sublimate. × 380.

FIG. 21. The anaplastic centre of the same tumour as in Fig. 20.

FIG. 22. *Astrocytome, giganto-cellulaire.* The tumour was a small nodule occurring in the wall of a large cerebellar cyst in an adult. Haematoxylin-eosin. × 300.

FIG. 23. A malignant pinealoma. Mitotic figures are abundant. Haematoxylin-eosin. × 540.



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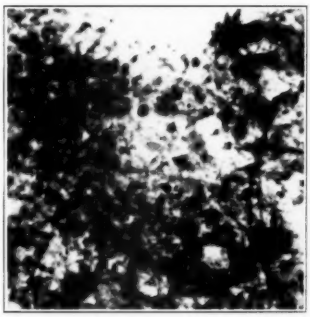

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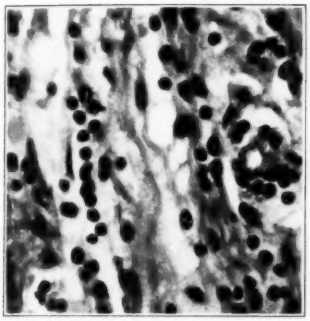

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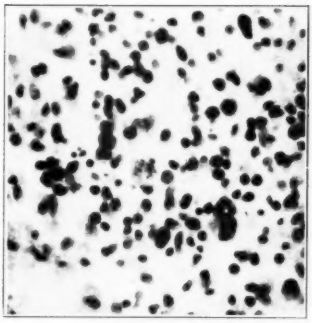

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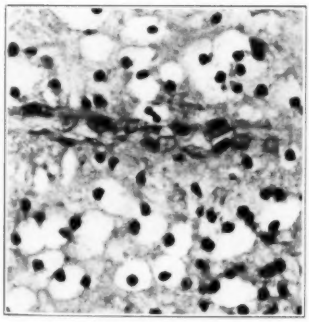

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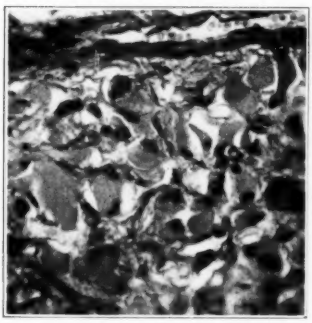

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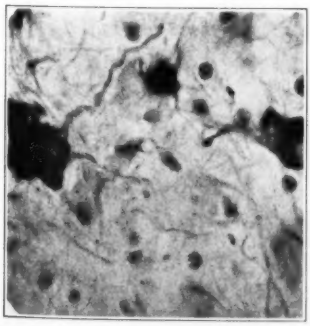

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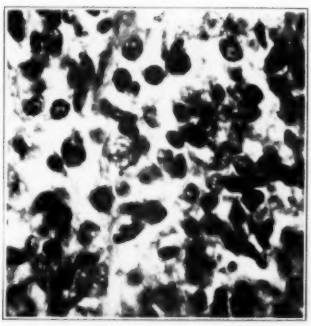

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PLATE 140

FIG. 24. Cells in a so-called ganglio-glioma of a frontal lobe. Pyridine silver. × 400.

FIG. 25. The cells of an astroblastoma showing how the nuclei may mimic those of nerve cells. Haematoxylin-eosin. × 480.

FIG. 26. Neuroblast-like cells occurring in a malignant tumour arising in the frontal lobe of a child. Haematoxylin-eosin. × 480.

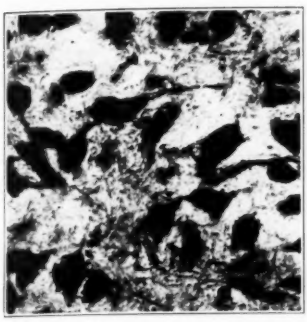
FIG. 27. Illustrating the neuroblast-like appearance that may be assumed by the nuclei of a rapidly growing tumour. The section is that of a sarcoma of the femur.

FIG. 28. Nerve fibres occurring deep within a cerebral astrocytoma of slow growth. The processes of the astrocytes are also faintly impregnated. Pyridine silver. × 400.

FIG. 29. Nerve cells and nerve fibres within a highly cellular glioma of the glioblastoma multiforme type. Silver carbonate. × 500.

FIG. 30. Nerve cells within a tumour removed from a child's cerebellum. The section closely mimicked the adult ganglio-neuroma. Silver carbonate.

FIG. 31. Degenerating nerve cells from the tumour shown in Fig. 30.



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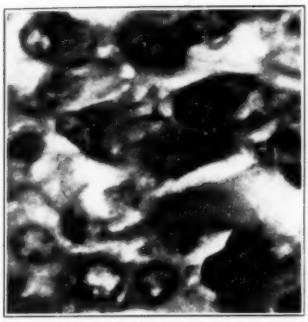

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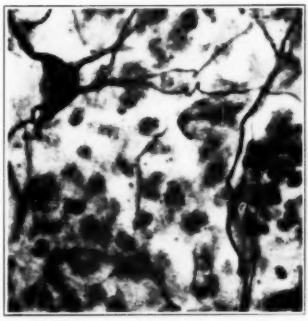

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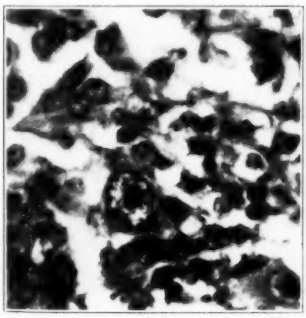

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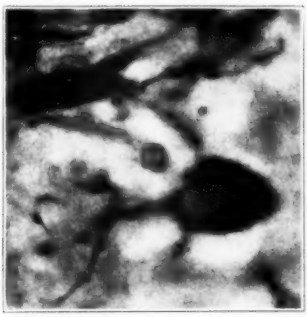

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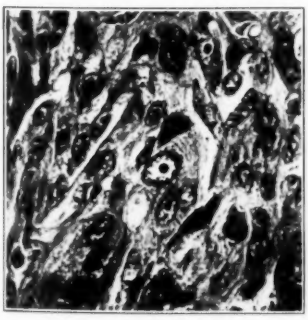

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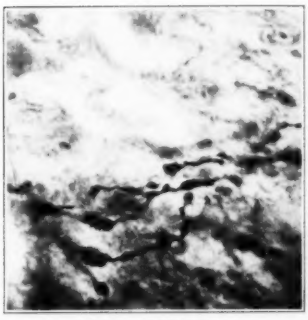

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PLATE 141

FIG. 32. Nerve fibres deep within a slowly growing cerebellar medulloblastoma. Pyridine silver. × 480.

FIG. 33. Nerve cells deep within a medulloblastoma. These were derived from a narrow strand of enclosed tissue. Haematoxylin-eosin. × 380.

FIG. 34. Giant cells in a glioblastoma multiforme. Haematoxylin-eosin. × 150.

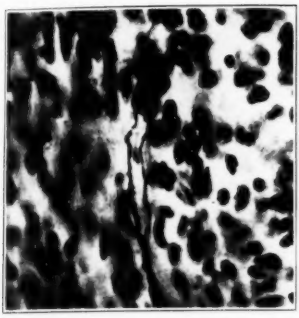
FIG. 35. A similar portion to Fig. 34, showing giant astrocytes. Gold sublimate. × 150.

FIG. 36. Giant astrocytes outside the edge of the same tumour. Gold sublimate. × 380.

FIG. 37. The same forms as inclusion cells at the margin of a vessel deep within the tumour. The transition could be clearly traced. Gold sublimate. × 380.

FIG. 38. A higher magnification of part of the astrocytic cuff. Gold sublimate. × 400.

FIG. 39. Astrocytes deep within a medulloblastoma. Gold sublimate. × 480.



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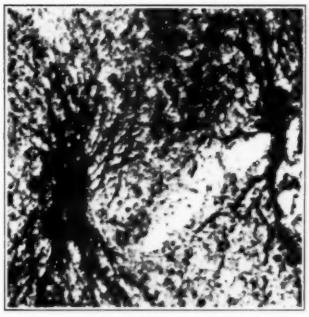

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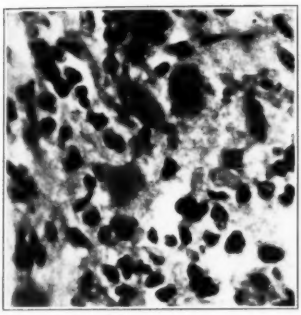

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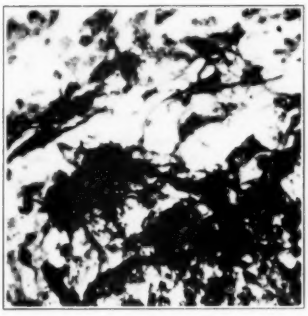

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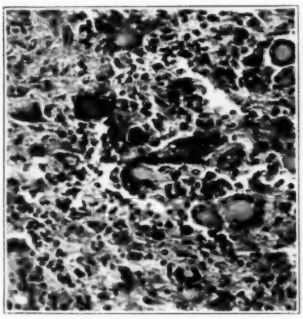

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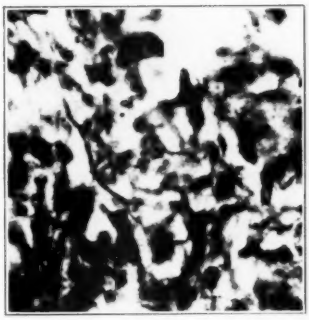

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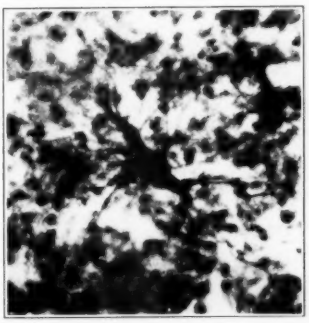

39

THE ORIGIN OF ONE TYPE OF SECONDARY PNEUMONIA *

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(From the Department of Pathology, Jefferson Medical College, Philadelphia, Pa.)

This discussion pertains to the development of pneumonia following pulmonary congestion and edema. Moon and Kennedy [1] have shown that marked congestion and edema, associated with capillary hemorrhages and increased concentration of blood, are found regularly in shock. The evidence is strong that such changes constitute the essential pathology of that type of circulatory failure. The capillary phenomena are most marked in the respiratory tract and result from atony of the capillaries and venules. Dale, Laidlaw and Richards [2] showed that histamine shock results from atony of capillaries and venules and Krogh [3] showed that capillary atony, increased permeability and edema are the characteristic effects of a wide variety of capillary poisons. Circulatory failure of this type is manifested clinically by a progressive decline in blood pressure, rapid respirations, rapid weak pulse, a decline in temperature and an increased concentration of blood. Pulmonary congestion and edema follow. Clinicians usually assign such circulatory failure to cardiac weakness, even though postmortem examination shows no gross or microscopic changes in the cardiac structure.

Circulatory shock or collapse develops characteristically following burns and other severe intoxications. Atchley [4] cited cases of diabetic acidosis and severe acute infections in which the shock syndrome was present. He considered these cases to be due to the same mechanism as in traumatic shock. He also reported a case of rattlesnake bite where the venom probably was injected directly into a vein. Characteristic shock-like manifestations resulted.

Krogh [3] believes that capillary atony results from various forms of toxemia, and produces circulatory shock in diverse clinical conditions. I have had occasion to substantiate this view by postmortem studies in such cases.[5] These have included intestinal obstruction, toxemias of pregnancy, burns, infections of unusual

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severity, intestinal perforations, hemorrhagic pancreatitis and poisoning with various drugs.[6] In each instance the gross and microscopic changes were identical with those present in traumatic shock, and included marked congestion and edema of the lungs. If the capillary atony and resulting deficiency of circulation are of marked degree the patient dies of circulatory failure with shock-like manifestations. If the circulatory deficiency is less extreme, but is sufficient to produce moderate pulmonary congestion and edema, the development of secondary pneumonia frequently occurs.

In lungs where the circulation is sluggish, capillaries and venules engorged, and where the alveoli contain albuminous fluid, ideal conditions are present for the development of infection. Various pathogenic organisms are present in the respiratory passages of the majority of persons, and fluid resulting from edema provides an excellent culture medium for their growth. Infection of the lung developing in this manner presents characteristics not found in primary lobar or lobular pneumonia. The lungs have a deep purplish red color (Fig. 1), are heavy, edematous, and contain irregular areas of consolidation which do not conform to the distribution of the bronchial branches. These areas vary greatly in size, distribution and number and are most numerous in the dependent portions Frequently there are scattered, imperfectly consolidated areas about 1 cm. in diameter. In other cases larger irregular patches occur. The character of the consolidation varies with the causative organism, the rapidity of the spread of the process and with the time elapsing before death. Occasionally the areas become confluent and resemble lobar pneumonia somewhat, except that they are mottled and mosaic-like in appearance and their density is less uniform. Bloody frothy fluid escapes from cut surfaces and from the smaller bronchi when pressure is applied. The bronchial mucosa is swollen and cyanotic in color. The pleural surfaces contain numerous minute areas of capillary hemorrhage. There are scattered areas of hemorrhage throughout the lung substance, and occasionally larger areas resembling hemorrhagic infarcts are seen.

Microscopic examination shows areas of leukocytic infiltration which varies greatly in density (Figs. 4, 5, 6 and 7). The capillaries and venules are dilated and engorged. Considerable fluid is present containing varying numbers of red cells from capillary hemorrhages. There is a deficiency of fibrin and the consolidation is less dense than

in primary pneumonias. The results of bacteriological examination are inconstant. Various organisms are found and cultures usually contain more than one type. Pneumococci, streptococci, staphylococci and *Micrococcus catarrhalis* predominate. Occasionally *B. influenzæ* and other bacteria are present.

Secondary pneumonia following burns is typical of the pneumonias that develop by the shock syndrome. The following case is illustrative. Three men were seriously burned following a collision in which a gasoline tank burst and was ignited. The burns were of the second and third degree, involving chiefly the legs, arms and face. Shock was a marked clinical feature in each case, but varied with each individual. The burns varied somewhat in the amount of skin involved. The man having the most extensive burn had a red cell count of 8,360,000 and the hemoglobin was 120+. The Dare hemoglobinometer which was used had no provision for higher readings. He died within forty-eight hours and the postmortem findings were typically those of shock. No pneumonia was present.

The second victim, whose burns were slightly less extensive, died of secondary pneumonia eleven days later. His condition of moderate shock, as shown by blood pressure, blood concentration and other clinical features, continued during the eleven days. At postmortem the lungs showed the characteristic features described for this type of pneumonia (Fig. 7).

The third man who was burned recovered. His condition of shock was less in degree and gradually subsided. The gradual recovery from shock is well illustrated by the changes in blood concentration on consecutive days:

Date	Specific gravity	Hemoglobin	Red cells
Dec. 14	1.075	120+	6,700,000
" 15	1.070	112	5,400,000
" 16	1.063	110	5,000,000
" 17	1.070	116	5,200,000
" 18	1.068	115	5,100,000
" 19	1.066	110	4,990,000
" 20	1.062	106	4,900,000
" 21	1.055	99	4,630,000
" 22	1.048	74	3,530,000
" 24	1.045	87	3,820,000

In material from 100 autopsies on adults secondary pneumonia occurred in sixteen cases. Congestion and edema of cardiac and renal origin were not included. Eight cases occurred following surgi-

cal procedures and one case each occurred in the following conditions: ulcerative colitis, acute hemorrhagic pancreatitis, drug poisoning (sedormide), obstructive jaundice, eclampsia, superficial burn of skin, diabetes with acidosis, and peritonitis. These presented the same type of pneumonia and were preceded by pulmonary congestion and edema in each case.

There is evidence that certain cases of pneumonia following influenza belong in this group. Many regard influenza as a systemic infection similar to measles and other exanthemata whose etiology has not been established. The severity of the disease in different epidemics and in different cases varies extremely. During the pandemic of 1918 in many of the most severe cases the individual died within two or three days of the onset of illness. These cases presented evidence of shock-like circulatory failure. There was a marked decline in blood pressure, weak pulse, rapid respirations and a decreasing temperature. Increased concentration of the blood was a prominent characteristic. Underhill and Ringer [7] made blood studies in forty-three cases. In the sudden, severe cases there was a marked concentration of blood with hemoglobin values ranging from 110 to 140. Death resulted in each instance. No concentration of blood was present in the less severe cases and there was no history of it among those who recovered. They concluded that the degree of blood concentration was an index of the severity of the illness, which was especially valuable in prognosis. They noted that the lungs in the fulminating cases were indistinguishable from those following lethal gas poisoning, and I have found them indistinguishable from the lungs following fatal burns. Postmortem examination showed wet bloody lungs and extreme capillary congestion of the mucosa of the pulmonary and gastro-intestinal tracts. There were numerous petechial hemorrhages in the mucous, serous and endocardial surfaces. Blood-tinged fluid was present in pleural and pericardial cavities. The lungs were increased 200 to 400 per cent in weight, due to marked edema and congestion. In the most severe cases no pneumonia was demonstrable, either grossly or microscopically. Apparently death took place from circulatory failure before the development of pneumonia occurred.

In cases of somewhat less severity the individuals lived from seven to fifteen days. On postmortem examination congestion and edema were not so extreme but were marked. Pneumonia of irregular type

and distribution was the characteristic feature. The lungs were heavy, wet and bloody and the consolidation varied greatly in character and extent. Bacteriological examination in such cases gave varying results. Organisms of the pneumococcic-streptococcic group occurred most frequently. In this particular the pneumonia following influenza does not differ from the group of pneumonias under consideration (Fig. 3). The view is widely accepted that it is a secondary infection, but the importance of capillary atony and resulting circulatory inefficiency in its development has not been emphasized. I have compared the gross and microscopic features of the lungs following influenza with those of secondary pneumonia following burns, and find no essential differences. It seems probable that their mechanism of origin is similar.

Summary

Various clinical conditions may result in a gradual failure of the circulation, which is not cardiac in origin but results from atony of the capillaries and venules. They include circulatory deficiency following extensive surgery, burns, various intoxications both metabolic and external in origin, abdominal conditions such as intestinal obstruction, pancreatitis, perforations, and severe systemic infections.

Marked pulmonary congestion and edema are characteristic features in these cases and increased concentration of blood is regularly associated with them.

One type of secondary pneumonia results from infection of such lungs with various organisms present in the respiratory tract.

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DESCRIPTION OF PLATES

PLATE 142

FIG. 1. Lung from a case of secondary pneumonia following drug poisoning. A man took an unknown quantity of sedormide. Profound narcosis was followed by circulatory failure ending in death four days later. Circulatory changes characteristic of shock, and irregular pneumonia in an early stage were shown at autopsy. Photographed with a normal lung (right) for comparison.

FIG. 2. Photomicrograph of lung from the same case. Edema and early pneumonia are present with marked dilatation and engorgement of capillaries and venules with capillary extravasation. A small amount of fibrin is seen, less than is found in primary pneumonias. × 500.

FIG. 3. Another field from the same lung as in Figs. 1 and 2, showing bacteria in the edema fluid. At the point marked X a dilated capillary has ruptured and red cells are escaping. Gram-Weigert stain, formalin fixation. × 1200.

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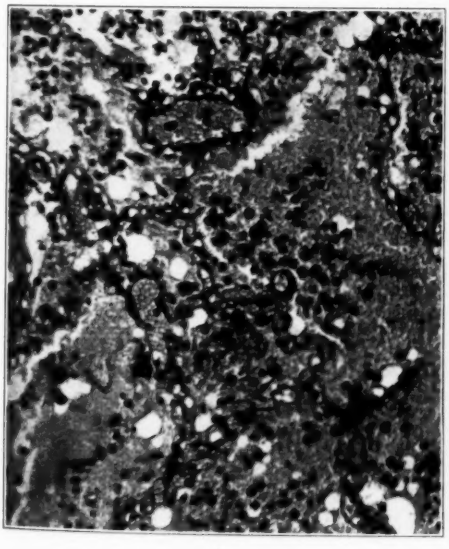

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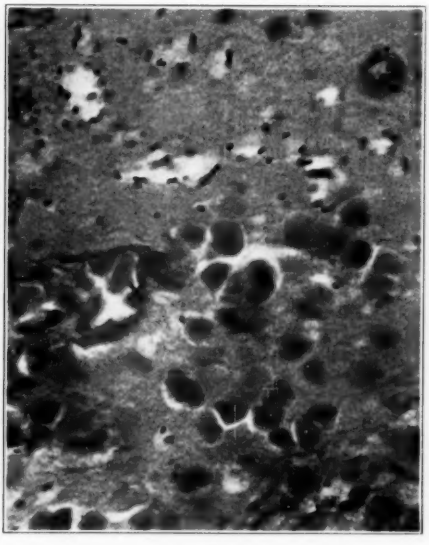


3

Moon

Origin of One Type of Secondary Pneumonia

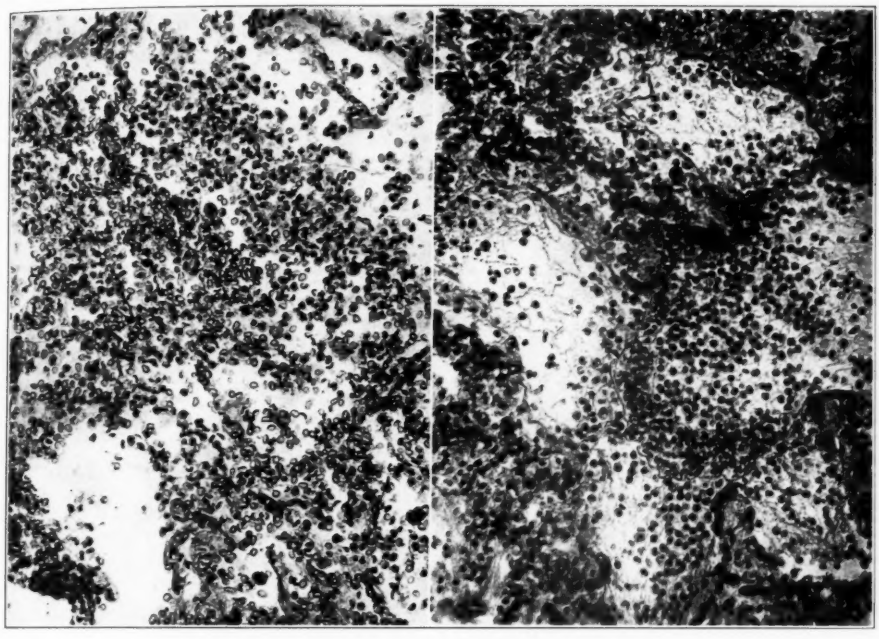
PLATE 143

FIG. 4. Early pneumonia from a case where the shock syndrome developed following mesenteric thrombosis. × 500.

FIG. 5. A more advanced stage of pneumonia from a case in which circulatory failure developed during a severe toxemia of pregnancy. × 500.

FIG. 6. An area of pneumonia in an engorged edematous lung from a case of severe influenzal infection. × 500.

FIG. 7. Pneumonia in an advanced stage. In this instance death took place from secondary pneumonia eleven days after an extensive superficial burn. The blood vessels are packed with corpuscles. In the center of the field is a capillary hemorrhage. × 500.



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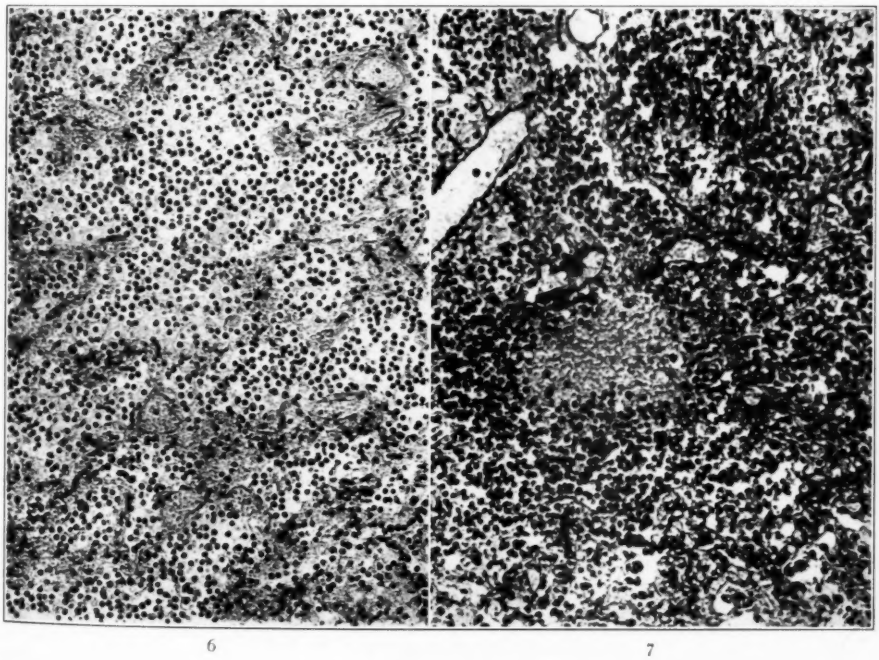

6 7

Moon

Origin of One Type of Secondary Pneumonia

FIBROMA OF THE BREAST *

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Benign neoplastic proliferations of the epithelial elements of the breast seem to furnish an incentive for neoplastic growth of the stroma. The name fibro-adenoma adequately expresses the structure of the resulting growth. The adjectives "pericanalicular" and "intracanalicular" further denote the relation of the component tissue elements. While fibro-adenoma of the breast is quite common, pure fibroma, *i. e.*, one containing no neoplastic epithelial elements, is rare. In fact, the case reported here is one of the few ever recorded.

REPORT OF CASE

Clinical History: Miss I. J. M., 47 years of age, a dietitian, was admitted to the New Haven Hospital on Sept. 15, 1932, complaining of a lump in the left breast. She stated that a small painless growth had been removed from the same breast in 1927. Subsequently a mass about 4 cm. in diameter recurred in about the same location underneath the skin 5 cm. above and lateral to the nipple, which was excised in May 1930. The microscopic structure of this growth was that of a fairly typical intracanalicular and pericanalicular fibro-adenoma of the breast (Fig. 1).

Several months prior to the present admission she again noted in the same breast a lump that gradually increased in size and was not tender or painful.

The patient appeared well nourished and apparently in good health. The systolic blood pressure was 120 and the diastolic 70 mm. Hg. The Kahn blood test was negative. The red blood cell count was 4,100,000 with 83 per cent hemoglobin, the white blood cell count was 8200, of which 69 per cent were polymorphonuclear leukocytes and 19 per cent lymphocytes. The urine contained no albumin or sugar.

In the upper outer quadrant of the left breast there was a firm, freely movable, well circumscribed mass measuring about 6 cm. in diameter. It did not involve the nipple and was neither fluctuant nor tender. The axillary lymph nodes were not enlarged.

On Sept. 16, 1932 the tumor was excised through an incision encircling the old operative scar. The gross appearance of the tumor on cut section resembled that of a fibro-adenoma, although the frozen section disclosed no epithelial elements. The operation was concluded by a conservative amputation of the breast, including the pectoral fascia.

* Received for publication June 8, 1933.

The specimen thus consisted of the tumor and the breast. The tumor presented a sharply demarcated, oval, firm, elastic, lobulated mass measuring 4 by 5 by 6 cm. It cut with increased resistance and a gritty sensation, disclosing smooth, glistening, pearly white surfaces with a pattern of interlacing strands and whorls. It contained no glandular or adipose tissue. The breast tissue proper measured 6 by 8 by 10 cm. The nipple and areola appeared intact. No masses were felt or seen anywhere.

Microscopic preparations stained with hematoxylin-eosin, Mallory's aniline blue, Mallory's phosphotungstic acid hematoxylin, and the Van Gieson method show the tumor to be composed of a fairly vascular, rather loose fibrous connective tissue containing no epithelial elements. It is surrounded by a thin but definite connective tissue capsule which separates the tumor from the surrounding normal breast tissue (Fig. 2). The cell nuclei and the fibrils run in interlacing streams and whorls. In some areas the connective tissue is as loose as embryonal tissue, in others it is fairly dense. The cell nuclei are spindle-shaped and are not hyperchromatic. Mitotic figures are scarce. No areas of necrosis are noted anywhere in the preparations.

The wound was nearly healed when the patient was discharged on Sept. 23, 1932. When last seen, eight months following operation, there was no evidence of recurrence of the growth.

Comment

In his monograph Williams [1] states that among the 2397 cases of mammary neoplasms in women analyzed by him there was one instance of this kind, a pure fibroma of the breast. He cites a specimen from Péan's collection, quotes from the pathological catalogue of the Hunterian Museum the description of three more specimens, and adds that Broca mentions having seen two cases of fibroma in the mammary region.

Suzuki,[2] in 1913, observed a tumor the size of a child's fist in the breast of a 43 year old woman. The tumor showed in parts the structure of a soft fibroma and in others that of a hard fibroma, and contained no glandular elements.

The next and most recent report of a case of pure fibroma of the breast also came from Japan and was made by Kon,[3] in 1931. The patient, a 33 year old housewife, mother of five children, noticed a

small tumor in the upper portion of the left breast six years prior to admission. This gradually enlarged to reach the size of an infant's head, but remained well circumscribed and movable. The breast was removed, together with the axillary lymph nodes. The tumor presented firm, uniform, fibrous, whorled, gray-white cut surfaces. Microscopic preparations show it to be composed of interlacing bundles of fibrous connective tissue containing no epithelial elements. There was no recurrence of the growth three years following operation.

Our case is of interest in that the breast on two previous occasions was the site of neoplastic growth. The structure of the tumor removed at the first operation we do not know. The growth removed at the second operation was a fibro-adenoma. The growth removed at the third operation was a pure fibroma in which the connective tissue closely resembled the connective tissue elements in the second growth. The question naturally arises whether there is any causal relation between these growths or whether they are independent tumors arising at different times in the same breast. The latter seems to be the more plausible explanation since there is no morphological evidence that any of these growths were malignant.

Summary

A pure fibroma of the breast, one of the few ever recorded, is reported. It occurred in a woman 47 years of age. The same breast on two previous occasions was the site of neoplastic growth. The structure of the tumor removed at the first operation is not known. The growth removed at the second operation was a fibro-adenoma. The one removed at the third operation was a pure fibroma in which the neoplastic tissue closely resembled the stroma of the second growth.

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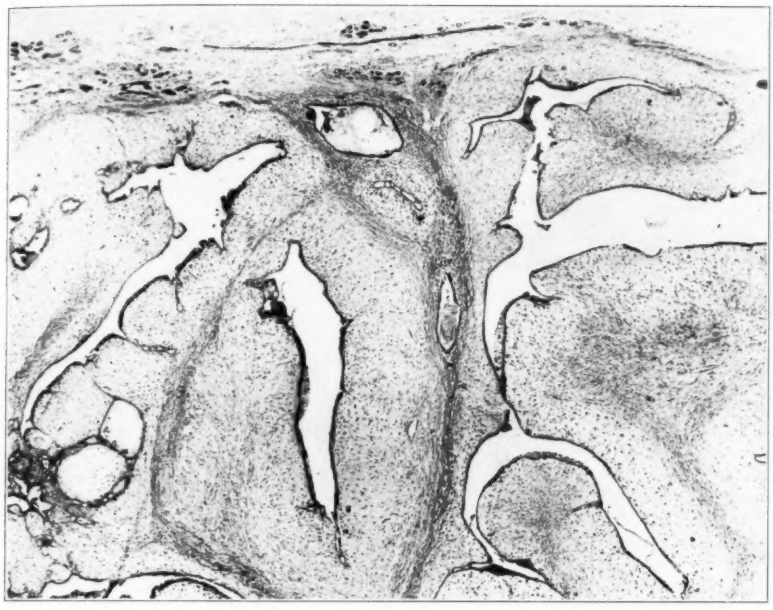
DESCRIPTION OF PLATE

PLATE 144

FIG. 1. Fibro-adenoma of the breast, pericanalicular and intracanalicular, removed at the second operation in 1930. × 25.

FIG. 2. Fibroma of the breast removed at the third operation in 1932. A thin but definite connective tissue capsule separates the tumor from the surrounding normal breast tissue. × 25.



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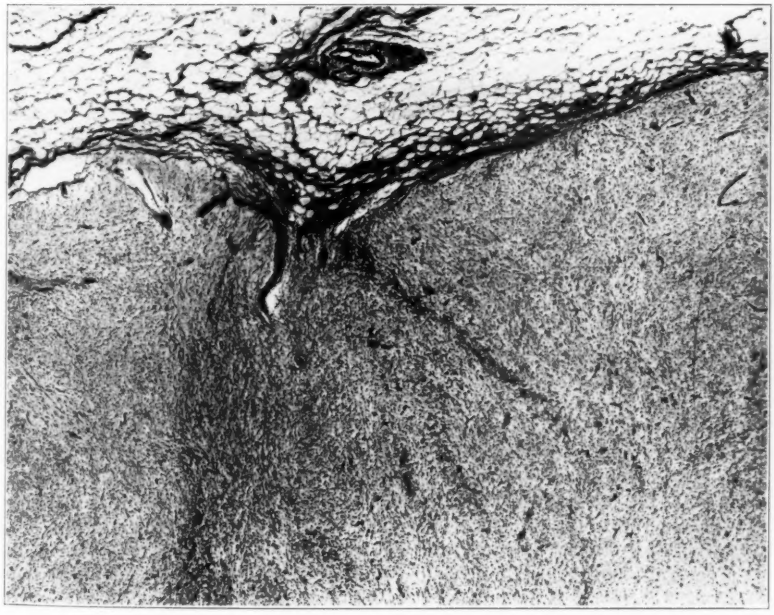

2

Halpert and Dial Fibroma of the Breast

UNIV OF WICH

LIPOSARCOMA *

REPORT OF A CASE WITH INTRACRANIAL METASTASES

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In a recent report of three liposarcomas apparently originating in bone Stewart [1] was scrupulously careful to avoid dogmatism in regard to the histological classification. He felt, however, that inasmuch as the lipoblast was the only cell within the bone marrow not represented in the group of primary tumors it was reasonable to expect that liposarcoma would occur in this location. Moreover, the natural history and histological characteristics of the tumors he described furnished additional tangible evidence of their right to be considered as belonging to a distinct entity.

Several qualities of these neoplasms may be taken as more or less characteristic. In regard to the clinical aspect of the picture it may be said that the tumors are relatively slow growing and that the duration of life usually is measured in years rather than months after the first appearance of the growth. Cranial metastases seem a common feature, if one may generalize on such a small series. Finally, the tumors appear to be quite sensitive to irradiation.

Examination of the specimens in gross showed them to be soft, yellow or reddish tumors, replacing bone but sharply demarcated at the margins. They were quite vascular and contained small hemorrhages within the substance of the tumor. In Stewart's three cases the tumors first appeared in a phalanx of the hand, in the fibula and in the femur. Sections showed the predominant cells to be large and arranged loosely or in an alveolar formation. The nuclei were relatively small, hyperchromatic and centrally or eccentrically situated. The abundant cytoplasm contained fine droplets of fat.

A review of the literature shows that no new cases have been reported since the appearance of Stewart's article. Bartlett [2] has reported two cases of periosteal lipoma, but these did not appear to

* Received for publication July 5, 1933.

involve the bone, though one of them had to be separated from the bone by "sharp dissection." It is noteworthy that the first surgeon dealing with one of Stewart's cases removed a tumor that he found closely adherent to the fibula. He considered it as closely applied to but not arising from the bone. However, the brief descriptions of the sections do not appear to identify the tumors with liposarcoma.

Dr. Bowman Crowell of the American College of Surgeons Registry of Bone Sarcoma has kindly forwarded records and preparations of two other cases provisionally classified as liposarcoma. Concerning one of these, No. 1383, there seems to be sufficient divergence of opinion to preclude its consideration here.

The other, No. 1224,* seems to belong more definitely to this classification. The patient was a white male, 60 years of age, who was admitted to the Rhode Island Hospital in a moribund condition and who died shortly afterward. Owing to his condition biopsy or operation was not performed. The only history available was that of loss of weight and pain in the right lower quadrant for a period of one year.

At autopsy two rounded, encapsulated tumor masses about 12 cm. in diameter were found extending from each side of the ala of the right ilium. The isthmus between these, about 6 cm. in thickness, destroyed the intervening ilium; there was also some invasion of the sacrum. The surface of the tumor appeared soft and yellowish. Hemorrhagic and necrotic areas were found on section. A careful search for metastases was unavailing.

Microscopically this tumor has a good deal in common with the one reported in this paper. The cell type is quite similar. The nuclei are often hyperchromatic, usually eccentrically placed, the cytoplasm abundant and finely granular. Fat stains (sharlach R) show considerable extracellular fat, with the cytoplasm of occasional cells taking the dye. There is more evidence in favor of neoplastic origin than in our case. The alveolar arrangement is poorly developed, though present in some areas, mitoses are frequent, there is considerable variation in the size and shape of the cells, and the bizarre forms are not uncommon.

In reporting the following case we feel the same reluctance that affected Stewart in regard to making a too positive diagnosis. Although it seems justified and is corroborated by eminently compe-

* This case was reported to the Registry by Dr. B. Earl Clark.

tent pathologists the report may be met with equally competent skepticism. Nevertheless, it seems worth while to record the tumor under the present heading, and to deal with the question of reclassification when it arises.

Some of the features of the cases reported, as well as our case, are given in the table.

TABLE I

Data on Cases of Liposarcoma of Bone

Case	Age	Sex	Primary site	Cranial metastases	Duration of illness	Subsequent course
I (Stewart)	*yrs.* 23	M	Phalanx hand	None	*yrs.* 4	Living 9 yrs. after admission
II (Stewart)	28	M	Fibula	Present	1	Died 5 yrs. after admission
III (Stewart)	28	M	Not found	Present	Unknown	Died soon after admission. Disease far advanced
IV (No. 1224)	60	M	Ilium	None	1	Died soon after admission. Disease far advanced
V (S. M. H. 48952)	23	F	? Fibula	Present	5	Living 22 months after admission

REPORT OF CASE *

Clinical History: Martha A. (S. M. H. 48952), a married, white female, 23 years of age, was admitted to the Strong Memorial Hospital June 25, 1931.

Five years before admission, in 1926, the patient had undergone an operation for extirpation of a tumor of the lateral aspect of the right lower leg. Preparations of the tumor were sent to Dr. F. B. Mallory for examination. One observer, upon examining sections of the tumor returned a diagnosis of "alveolar carcinoma." Dr. Mallory states that his original opinion was that the tumor was a metastatic hypernephroma. Following operation the leg was treated once with radium. It should be made clear that we do not have any record that the tumor was attached to the fibula or its periosteum, though it must have been in close proximity.

The patient entered the hospital because of headaches that had begun six months previously. Her history was characteristic of increasing intracranial tension. Beginning with headache, the illness was successively complicated by progressive loss of vision, pain in both shoulders and paresthesias affecting both

* I am indebted to Dr. W. P. VanWagenen for permission to report this case.

hands. Three months before admission dizziness and left-sided tinnitus appeared, and the illness culminated, a few days before admission, in the development of projectile vomiting. No loss of weight was reported, and a review of the cardiorespiratory, gastro-intestinal and genito-urinary systems failed to disclose further symptomatology. The family, marital, and past history contributed nothing of interest.

Physical examination showed the patient to be well developed and well nourished. The lungs and heart were considered normal. Careful examination of the abdomen and back in the region overlying the kidneys failed to show evidence of a neoplasm. The routine neurological examination was entirely negative. Ophthalmoscopic examination, however, showed bilateral choking of the nerve heads of approximately six diopters, secondary optic atrophy, marked venous engorgement and small, scattered hemorrhages. The visual fields were concentrically constricted and exhibited a left temporal defect that was thought to be due to dilatation of a retinal vein.

The patient's hemoglobin level, white and red cell counts and urinary findings were within normal limits. Blood Wasserman test was negative. Roentgenograms of the chest and skull showed no metastases.

Two days after admission a ventriculogram was carried out which showed a slight shift of both ventricles toward the right and a deformity of the left anterior horn that suggested a mass encroaching upon it from above. At the same session a left frontal bone flap was turned down. The exposed dura was tense and thinned, but the tumor was not evident upon the surface of the cortex, nor was the surgeon able to strike either tumor or cyst with the exploring brain needle. The operation was terminated at this time because of the patient's unsatisfactory condition, but she was left with an ample decompression, and other measures were instituted to reduce intracranial tension.

Twelve days later, July 9, 1931, the left frontal bone flap was re-elevated and an incision was made in the second left frontal convolution. At a depth of approximately 4 cm. the tumor was exposed and it proved to be a discrete, soft, reddish gray mass, roughly elliptical in shape and approximately 4 cm. long. It was removed without great difficulty.

The patient's postoperative course was quite satisfactory; vision improved rapidly, and the motor aphasia that had appeared following the first operation gradually cleared up. The patient left the hospital July 31, 1931, twenty-two days following the operation.

As this paper is submitted the patient is living, but is suffering from intracranial recurrences. Relief seems to have been afforded, at least temporarily, by X-ray therapy, since these recurrences gave evidence of their existence nine months ago.

Gross Description of Tumor: The pathological report on the formalin-fixed material reads as follows: "The specimen consists of a rounded mass of white tissue measuring 2 by 3 by 3.5 cm., which is enclosed in a delicate fibrous capsule. There are many small blood vessels on the surface, which is of irregular contour owing to the projection of numerous small, rounded nodules. The tumor is of a rubbery consistence and cuts easily to present a smooth white sur-

face, dotted by a number of small, irregularly shaped hemorrhagic areas."

Microscopic Examination: Microscopic sections show vascular neoplastic tissue. The tumor cells are arranged in closely approximated small rounded groups and columns incompletely separated from one another by narrow strands of small flattened cells. There are several clear spaces of moderate size and cystic appearance which contain blood cells; in the majority of these, endothelial lining cells are not observed.

The tumor cells are large and round or polyhedral, with distinct cell membranes and abundant granular cytoplasm showing variation in depth of staining in different cells. An occasional cell contains in its cytoplasm a rounded, clear vacuole. The nuclei are large, round or oval, pale and vesicular with prominent nucleoli. The situation of the nuclei tends to be eccentric, and they lie frequently at the extreme edge of the cytoplasm. Mitotic figures are not numerous. No groups of adult fat cells are present.

Sections of formalin-fixed tissue stained for fat show moderate numbers of small red granules in some of the cells, while in the majority, deposits of fat which stain with Sudan III are not demonstrable.

Discussion

The tumor was felt to be a metastatic liposarcoma. Sections were seen subsequently by Dr. F. B. Mallory, an excerpt from whose communication regarding them follows: "The best diagnosis is liposarcoma, metastatic from tumor of leg. . . . None of the cells differentiate into adult fat cells but they have the granular cytoplasm, eccentric nuclei, and alveolar arrangement which are considered characteristic." Dr. F. W. Stewart also concurred in the diagnosis, and the consensus among Drs. James Ewing, S. B. Wolbach, and J. J. Morton, who saw sections of the tumor, was that the diagnosis of liposarcoma was justified. Dr. G. H. Whipple considered the possibility of an endothelial tumor arising from blood vessels as likely.

When sections from a block of the original tumor of the leg were compared with the intracranial tumor it was Dr. Mallory's opinion that the two tumors were of identical structure. Our observations bear out this opinion. The five-year period intervening between the

excision of the tumor of the leg and the intracranial metastases argues strongly against the validity of the early diagnoses of hypernephroma and alveolar carcinoma. It is of interest that one of Stewart's cases was first diagnosed "alveolar sarcoma."

Photomicrographs of sections are reproduced to show the microscopic anatomy of the tumors, and the apparent identity of the original neoplasm with the intracranial rumor.*

Summary

A case of liposarcoma with late intracranial metastases is reported. The few cases available for study seem to indicate that these tumors grow slowly, are radiosensitive, metastasize late and show a tendency to metastasize to the cranium.

The author wishes to thank Dr. F. B. Mallory for permission to use his preparations of the original tumor and for his comments on the case.

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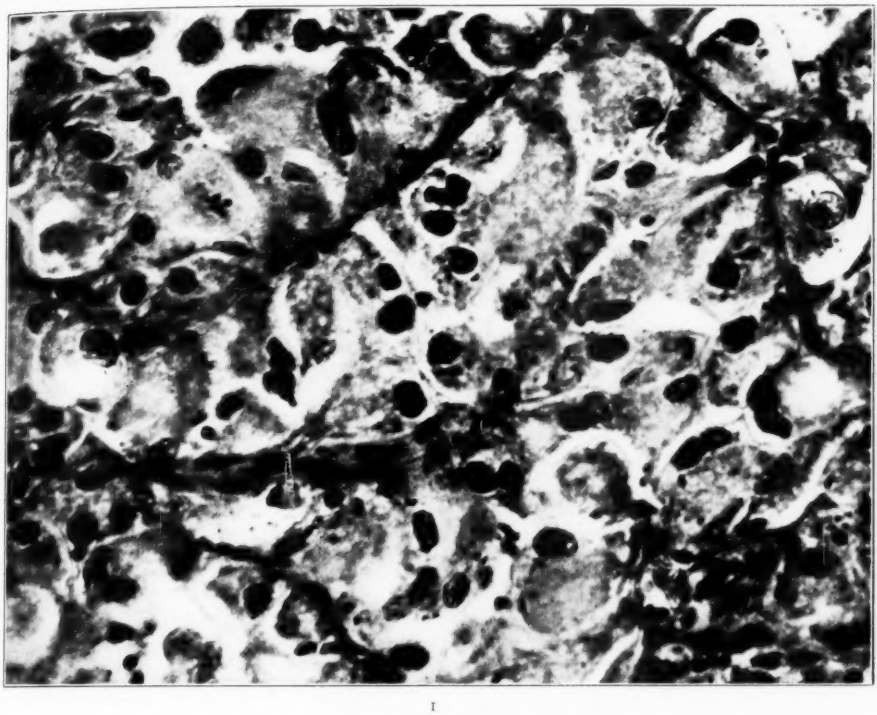
DESCRIPTION OF PLATE

Plate 145

Fig. 1. Photomicrograph of the primary tumor of the leg showing a rapidly growing liposarcoma of embryonic type. One mitotic figure is present. × 500.

Fig. 2. A corresponding picture from the intracranial tumor, showing a similar type of new growth, evidently a metastasis. × 500.



1

2

Fender Liposarcoma

THE pH OF FORMALIN — A FACTOR IN FIXATION *

ADJUSTMENT AND STABILIZATION OF THE HYDROGEN ION CONCENTRATION OF FORMALIN SOLUTIONS

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The appreciation of acidity and alkalinity as factors in biological staining is almost as old as staining itself. Goeppert and Cohn,[1] in 1849, made the first attempt at differentiating tissues in plants by staining with carmine. The addition of ammonia to carminic acid by Hartig,[2] in 1854, was found valuable in differentiating the nuclei in plant cells. Ammonia was likewise employed by Gerlach,[3] in 1858. Thiersch,[4] in 1865, observed that carmine with oxalic acid produced an orange stain and with ammonia a violet stain.

It was F. Blum,[5] in 1893, who first employed formalin solutions for hardening and preserving tissue for histological technique. He obtained his best results with 10 per cent formalin (1 part of commercial formalin to 9 parts of water).

Soon after the introduction of formalin as a fixative, attempts were made to neutralize the solution. G. Mann,[6] in 1894, added either sodium or magnesium carbonate to formalin with the hope of neutralizing the acid content. Up to the present time many reagents have been employed to correct the acidity of formalin. The following are those most commonly used: sodium carbonate, magnesium carbonate, calcium carbonate, lithium carbonate, magnesium oxide, ammonia and sodium hydroxide. Atkins,[7] in 1922, suggested the use of borax. It occurred to the author that pyridine, because of its chemical properties, would be a more suitable reagent.

In the preparation of so-called neutral formalin the fundamental concept of base neutralizing acid has been in the minds of several masters of histological technique. However, in preparing such a formalin solution it is essential to consider the nature of formaldehyde, as well as that of the reagent employed. All dilutions of commercial formaldehyde in distilled water are acid. In addition, there are present several factors that tend toward acidification: (*a*) pro-

* Received for publication June 27, 1933.

duction of formic acid upon the oxidation of formaldehyde; (*b*) absorption of carbon dioxide from the air; and (*c*) liberation of acid from the tissue immersed in the solution. Furthermore, commercial formalin usually contains methyl formate, the saponification of which would also tend to depress the pH of solutions to which base is added. When base is added to an aqueous solution of formaldehyde an increase in pH results. However, a decrease in pH follows.

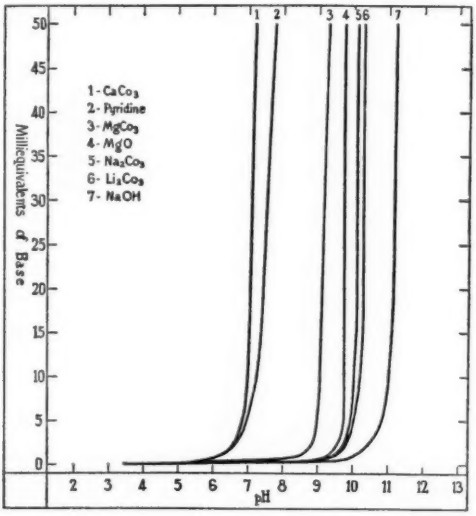

CHART 1

This lowering of the pH cannot be entirely checked, but the speed at which acidification becomes manifest can be affected by the addition of an excess of the reagent employed. The addition of an excess of base, if approximate neutrality be desired, necessitates a consideration of the maximum buffering range * that will obtain when the selected reagent is dissociated in an aqueous solution of formaldehyde. It is this that determines the range of maximum stability of the pH of the fixing fluid.

Chart 1 presents a comparison of the maximum buffering ranges that obtain upon the addition of the several reagents in common use

* By buffer action is meant the resistance to change of pH exhibited by a solution when it is subjected to gain or loss of acid or alkali, according to Clark.[8] The pH range at which this resistance to change takes place is known as the maximum buffering range.

to 25 per cent commercial formalin in distilled water. Each pH determination was made on individual samples of 100 cc. of 25 per cent commercial formalin in distilled water, to each of which was added a definite quantity of one of the several reagents employed. The pH determinations were made by the Glass Electrode within one hour after the addition of each reagent. It is obvious that with the exception of calcium carbonate the common reagents buffer best at pH values well above neutrality. This means that such a concentration of base as will produce neutrality will not produce a stable solution. In the same figure we find also that pyridine or calcium carbonate might be added in excess without causing a marked rise in pH. Conversely, an excess having been added, consumption of either pyridine or calcium carbonate is accompanied by a very slight decrease in pH. It is this feature of the latter that makes them the reagents of choice when relatively stable neutral formalin is desired.

The author has selected pyridine, instead of calcium carbonate, for several reasons. Pyridine-formalin is a relatively stable solution without a precipitate and void of all alkali earth metals, which appear to be objectionable elements in subsequent silver staining. Ammonia will not serve the same purpose as pyridine because it reacts with formaldehyde to form the very weakly basic condensation product hexamethylenetetramine. Formalin solutions that have been adjusted to pH values in the alkaline range by addition of ammonia, therefore, regain part of their acidity on standing, the pH level sinking below pH 7.0. Pyridine, being a tertiary base, is unable to undergo any such condensation with formaldehyde. In addition, the properties of pyridine itself are most desirable in fixation. Pyridine has long been recognized as a hardening, dehydrating and clearing agent. Furthermore, the formation of paraformaldehyde, an undesirable precipitate, seems to be checked if not completely avoided in pyridine-formalin.

Chart 2 indicates the effect of pyridine on the pH of 25 per cent commercial formalin to which it is added. I have found that pyridine-formalin made up as follows is most satisfactory for fixation of tissue:

Distilled water	75 cc.
Commercial formalin	25 cc.
Pure pyridine	5 cc.

Tissue should be immersed in approximately 20 times its weight of pyridine-formalin. Forty-eight hours is sufficient time for fixation. In preparing tissue for peripheral nerve stains 2 weeks is preferable. No injury to tissue has been noticed after 6 months immersion in pyridine-formalin, and the formation of formalin pigment has been prevented. Tissues so fixed are suitable for all the usual

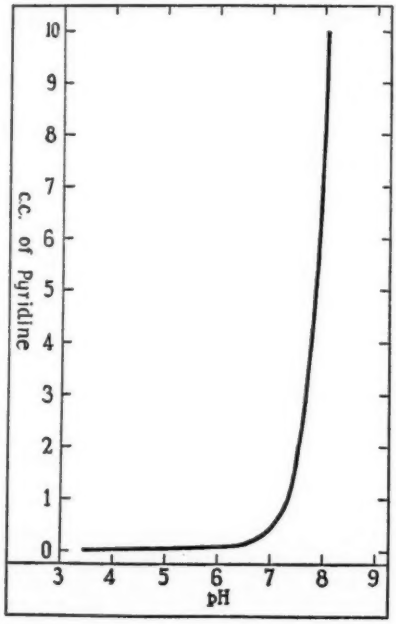

CHART 2

stains, such as hematoxylin and eosin, the Masson-Mallory trichrome, fat stains, the Laidlaw collagen-reticulin stain, the dopa reaction, and so on. Pyridine-formalin has proved to be far superior to all other fixing fluids in preparing tissue for the Laidlaw modification of the Gros-Bielschowsky silver stain for neurites in frozen sections.[9]

Embryonic bone and the bone that is formed in tissue culture are susceptible to even a low degree of acidity in the fixing fluid. Hence alcohol or neutral formalin are the only available fixatives for this material. And, since in work with experimentally produced bone it

is desirable to avoid the presence of the alkali earth metals in the fixing fluid, pyridine-formalin affords a convenient and easy solution of the formalin problem (Murray [10]). In tissue culture fixation a 5 per cent pyridine-formalin solution is used. This may be prepared by diluting 1 part of the standard 25 per cent pyridine-formalin solution with 4 parts of either distilled water or normal saline solution.

The following table presents a series of determinations made on routine surgical specimens fixed in 25 per cent pyridine-formalin.

TABLE I

Serial No.	Laboratory No.	Surgical specimen	Fluid-specimen ratio	Time	pH	pH change
				days		
1	51726	Hernial sac	28.5 –1	9	7.62	–0.19
2	51730	Thyroid	2.5 –1	8	7.04	–0.77
3	51739	Testicle and hernial sac	1.9 –1	6	6.81	–1.00
4	51748	Breast	1.7 –1	5	7.00	–0.81
5	51754	Hemorrhoids	21.2 –1	4	7.63	–0.18
6	51755	Hemorrhoids	25.0 –1	4	7.63	–0.18
7	51765	Abscess right leg	12.5 –1	3	7.32	–0.49
8	51768	Thyroid	1.8 –1	1	6.99	–0.82
9	51770	Cervix	3.6 –1	7	7.08	–0.74
10	51771	Colostomy	7.2 –1	1	7.50	–0.31
11	51778	Tumor bronchial region	12.5 –1	7	7.55	–0.27
12	51784	Dermoid cyst	16.6 –1	6	7.55	–0.27
13	51796	Thyroid	1.5 –1	5	6.99	–0.83
14	51805	Thyroid	5.4 –1	4	7.16	–0.66
15	51806	Thyroid	1.1 –1	4	6.85	–0.97
16	51812	Cervical lymph nodes	11.7 –1	3	7.44	–0.38
17	51821	Curettings from femur	12.4 –1	3	7.59	–0.23
18	51827	Hemorrhoids	19.5 –1	2	7.65	–0.17
19	51831	Appendix	4.4 –1	8	7.16	–0.66
20	51832	Appendix	7.3 –1	8	7.44	–0.38
21	51833	Hemorrhoids	17.4 –1	8	7.59	–0.23

In Table I we find that only a slight change in pH takes place over a variable period of time. After tissue has been fixed (24 to 48 hours) the pH drop is practically checked. It is obvious that the fluid-specimen ratio (cc. of fluid to gm. of tissue) is an important factor. If the recommended 20 to 1 ratio be followed, the drop in pH will usually be not more than 0.3 of a pH unit over a period of fixation.

Finally, pyridine-formalin is the fixative of choice whenever neutral formalin is desired, and since such formalin is optimum

for fixation, pyridine-formalin for fixation of tissues in general is recommended.

NOTE: It is a pleasure to thank those whose advice and coöperation have been valuable factors in preparing this paper, among them Prof. Arthur Purdy Stout, director of the laboratory, and Dr. Margaret R. Murray of the department of surgery, Profs. H. T. Clarke and E. G. Miller, and Mr. F. Rosebury of the department of biochemistry. The writer is especially indebted to Dr. George F. Laidlaw of this laboratory who has given generously of his time and of his rich experience in histological technique.

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SCIENTIFIC PROCEEDINGS OF THE THIRTY-THIRD ANNUAL MEETING OF THE AMERICAN ASSOCIATION OF PATHOLOGISTS AND BACTERIOLOGISTS

WASHINGTON, D. C.
May 9 and 10, 1933

THE AMERICAN ASSOCIATION OF PATHOLOGISTS AND BACTERIOLOGISTS

ABSTRACT OF BUSINESS SESSION

The following officers were elected at the meeting May 9, 1933:

President	O. T. Avery
Vice-President	William Boyd
Treasurer	F. B. Mallory
Secretary	Howard T. Karsner
Incoming Member of Council	E. R. Long
Assistant Secretary	Robert A. Moore

ABSTRACT OF MEETING OF THE COUNCIL

Voted to elect the following new members:

John T. Bauer	Frederick C. Narr
Thomas H. Belt	James M. Neill
Robert M. Choisser	James L. O'Leary
Herman R. Churchill	Frank B. Queen
Robert S. Cunningham	Herbert L. Ratcliffe
William A. DeMonbreun	Harry L. Reinhart
Vera B. Dolgopol	Arnold R. Rich
Robert C. Grauer	Thomas M. Rivers
Eleanor M. Humphreys	Florence R. Sabin
Raymond A. Kelser	Grace M. Sickles
Eric A. Linell	John W. Spies
Ralph E. Miller	Harold L. Stewart

Voted to accept with regret the resignations of Drs. H. L. Amoss, A. J. Chesley, Stanley Cobb, S. J. Crowe, I. C. Hall, A. T. Hess, J. A. Kolmer, S. H. McKee, R. G. Mills, A. G. Nichols, T. P. Sprunt, Ruth Tunnicliff, G. H. Weaver, Toynbee Wight, and R. T. Woodyatt.

Voted to elect Frederic Parker, Jr. as Assistant Editor of the *American Journal of Pathology*.

Voted to authorize the Editorial Board to issue a special number of the *American Journal of Pathology* in honor of Dr. Frank B. Mallory.

Voted to appoint Drs. Ewing, Callender and Mallory a committee on the publication of the report of the Registry of Lymphatic Tumors, with power to act.

Voted to select as a symposium topic for 1934 the subject of arteriosclerosis and to request Dr. Oskar Klotz to serve as referee.

The Secretary was directed to place in letters of acceptance of resignations a statement that the Council would gladly consider reinstatement at any time the person sees fit to notify him that he wishes reinstatement.

Voted to adopt the following resolution:

> The American Association of Pathologists and Bacteriologists expresses entire sympathy with the Medical Library Association in its protest against the cost of German medical periodicals and will, in so far as possible, engage to support any means that may be adopted to enforce action by the German publishers.

Voted to accept the invitation of the University of Toronto and to meet in Toronto March 29 and 30, 1934.

AMERICAN ASSOCIATION OF PATHOLOGISTS AND BACTERIOLOGISTS

A Unique Infection in Man with a New Yeast-Like Organism. G. H. Hansmann and (by invitation) J. R. Schenken, Iowa City, Iowa.

Abstract. A white man, 43 years of age at the time of death, had had an irretractable skin affection during the last 16 years of his life. His residence during this entire period was in Iowa. The first lesions were noted in 1916 on the skin in back of the knees. The extension of the disease was gradual and by 1929 the entire skin was involved by a scaly dermatitis, underneath which the skin was somewhat thickened and reddened. The peripheral lymph nodes became enlarged, the larger nodes measuring 3 cm. in diameter. During 1929 the skin became more reddened and thickened and cracked easily. In June, 1932, the lesions became papular in character, so that by July the skin was thickly set with hard, umbilicated papules that measured 0.5 cm. in diameter. He developed a high fever late in July, which was associated with evidence of pleurisy and a systemic infection. Death occurred Aug. 7, 1932.

A papule and a lymph node were removed during life for study. Both contained an organism that appeared as a small yeast. It was situated largely within large mononuclear leukocytes and giant cells. There were no intraepithelial abscesses. The organism measured 5 microns, while the yeast-like cell proper measured 3 microns. Postmortem examination revealed localization of the organism in the lungs and adrenals, in addition to the skin and lymph nodes.

The organism had no particular food requirements. The appearance, after 6 days, of flat, icy-appearing, filamentous specks on the surface of the medium was characteristic of the early colonies. The medium was not deeply invaded. Sugars were not fermented. The characteristic finding was numerous, large, spiculated chlamydospores. They appeared on lateral branches near the center of the colony.

The organism was pathogenic for guinea pigs, rabbits, rats and dogs. The dog was particularly susceptible. Generalized lesions were seen in this animal 4 weeks after an intravenous inoculation. These lesions were largest in the lung and spleen. The yeast-like organism was isolated from the various organs.

The spiculated chlamydospore is distinctive. The yeast-like organism in tissues is smaller than any described heretofore. The character and distribution of lesions in man are unlike those of any other disease. The organism is a member of the genus *Sepedonium*. So far as we are able to tell, it is the first pathogenic member of this group.

The Pathological Anatomy of Actinobacillosis in Man and Experimental Animals. D. C. Beaver, Rochester, Minn.

Abstract. Previous instances of human infection by the *Actinobacillus*, namely, the case of meningitis reported by Rivout and Pinoy, and the case of *Actinobacillus* bacteremia reported by Thompson and Willius, afforded no opportunity for pathological investigations, since these cases terminated in recovery. This, the third human case to be reported, is the first to result in death and therefore the first upon which pathological study has been made.

Although the exact nature of the lesions of human actinobacillosis has been unknown, their characteristics might have been anticipated from a study of the lesions in cattle, where the disease frequently occurs spontaneously. Bovine lesions are essentially chronic granulomatous abscesses, in the exudate of which pseudosulphur bodies are found. The sulphur granules of bovine actinobacillosis are composed of closely set, small Gram-negative bacilli in ball-like colony formation, surrounded by radiating pseudoclubs. They are never composed of entangled masses of Gram-positive mycelia with peripheral radiating clubs, as in actinomycosis.

The human lesions, as exemplified by this case, were multiple, discrete, granulomatous abscesses and involved the liver, spleen and lungs. The spleen was most severely affected and weighed 748 gm. The abscesses were composed either of thick creamy pus, or more frequently of material of thick pasty consistence, resembling caseation necrosis. Microscopically the lesions were focal and sharply circumscribed. The central portions were usually composed of granular, acellular, eosin-staining material in which fragmented nuclear remnants were prominent. Polymorphonuclear leukocytes were abundant in a zone peripheral to the central necrosis. An outermost zone was composed predominantly of endothelial cells and fibroblasts. The lesions were avascular. Masses of bacteria in ball-like colony formation were frequently associated with the layer of polymorphonuclear leukocytes. They resembled the central portion of the "sulphur granules" as found in bovine actinobacillosis, but peripheral clubs were never found in the human tissues.

The organisms, as recovered from the human lesions, and from the ante mortem blood culture, were proved to be pathogenic for rabbits, guinea pigs and mice. Granulomatous abscesses and tubercle-like granulomata were formed. In the lesions of experimental animals the granulomatous features were frequently much more prominent than they were in human lesions; nevertheless, they were similar to if not identical with one another. Bacterial masses, in ball-like colony formation, were found in many of the infectious foci of the experimental lesions. Peripheral clubs were never present, as in bovine actinobacillosis, although suggestions of early pseudoclub formations were sometimes observed.

ACTINOMYCOSIS OF TUBES AND OVARIES. V. H. Cornell, Washington, D. C.

Abstract. The literature of actinomycosis, in which cases of the internal female genitalia were involved, has been reviewed to date. There have been 66 cases reported, the author's bringing the total to 67. The longest previously reported cure was 3 years and 1 month; the individual in the case here reported has now been entirely well for 4 years.

The case presented was that of a white woman, 31 years of age, who had had pain in the right lower quadrant since 1919. Appendectomy was performed Aug. 10, 1924, but no histological record is available. Pain recurred and continued until acute illness caused admission to the hospital May 3, 1929. Partial intestinal obstruction and a mass in the right pelvis were the preoperative diagnoses. Adhesions were broken and a right tubo-ovarian mass was removed. Colonies of actinomyces in an enlarged ovary and an attached tubal mass were found histologically in the midst of multiple communicating abscesses, all enmeshed in dense fibrous tissue. No cultures were made as the nature of the condition was not recognized until sections were studied.

Discussion

(Dr. Esmond R. Long, Chicago.) It was not clear to me what was the source of the infection. How did it arise in this location?

(Dr. Cornell.) I presume that it was possibly appendiceal in origin. I tried to get the appendix, which had been previously removed, but no sections had been made and the gross specimen had been discarded.

(Dr. Long.) That would be the most likely source.

(Dr. Cornell.) It seems to me to be the most likely.

TUBERCULOUS ENDOPHLEBITIS WITH OBLITERATION OF THE SUPERIOR VENA CAVA. REPORT OF A CASE. H. C. Schmeisser, Memphis, Tenn., and (by invitation) Henry Fuller, Mulberry, Fla., and I. H. Jones, Paris, Tenn.

Abstract. This condition is not only very interesting but extremely rare. We have found only one case in the literature, that reported by Prof. Guido Banti in 1891. His case was a male, aged 46 years, a native of Florence, who at autopsy showed the superior vena cava to be converted into a hard cylinder with a vegetative mass occupying its auricular entrance, which microscopically and bacteriologically proved to be a tuberculous endophlebitis. No clinical record of importance was obtained.

Our case occurred in a female, aged 24 years, a negress. The clinical record was complete. The heart at autopsy showed the lower part of the left internal jugular, both innominates, except for a small superior part of the right, and the entire superior vena cava to be completely obliterated by a tuberculous endophlebitis without thrombosis. The auricular orifice of the cava was completely covered by endocardium. Tubercle bacilli were demonstrated in sections of the intimal lesion. The enlarged right innominate vein pressed on the recurrent laryngeal nerve and the cava slightly compressed the right bronchus. The left common carotid artery took origin from the innominate artery 0.5 cm. above the origin of the latter from the arch of the aorta. The inferior vena cava was dilated.

The obstruction involved the entrance of the right and left inferior thyroid and internal mammary, left vertebral, subclavian and highest intercostal, and azygos veins. It was necessary for the blood from the head, neck, arms and thorax to return to the heart by means of a collateral circulation and the inferior vena cava.

The entire systemic venous circulation, except that of the heart, was in a state of chronic passive congestion and many normally insignificant veins had become prominent. This explained such symptoms as dyspnea, orthopnea, cyanosis and dropsy. Hoarseness and cough were due to pressure of the enlarged right innominate vein on the right recurrent laryngeal nerve.

The anomaly of the left carotid artery taking origin from the innominate artery might suggest that the closure of the auricular orifice of the superior vena cava was congenital. Could the patient have had her abnormal circulation for 24 years? After a congenital closure, tubercle bacilli from the focus in the lung or pleural cavity could have entered the circulation and could have settled out from the blood into the superior vena cava, causing the endophlebitis. This might explain the occurrence of a tuberculous endophlebitis of the superior vena cava, which must be considered very rare.

CULTIVATION OF ACID-FAST BACTERIA IN CHICK EMBRYO. Elizabeth Verder (by invitation) and Earl B. McKinley, Washington, D. C.

Abstract. Data are presented on the cultivation of several acid-fast bacteria in minced chick embryo in Tyrodes's solution, with and without the addition of 3 per cent glycerol. Comparisons are made with several of the cultures employed with cultivation on the ordinary laboratory media usually used for acid-fast organisms. The organisms studied include fresh human strains of *B. tuberculosis*, a bovine strain of *B. tuberculosis*, a freshly isolated strain of avian *B. tuberculosis*, strains R1 and H37 of *B. tuberculosis*, 4 strains of *B. leprae* recently isolated by us from fresh leprosy nodules, and the Duval and Kedrowski strains of so-called *B. leprae*. Data are also given on the cultivation of several of these strains on the oyster-egg medium recently described by us. In general, with the various strains of *B. tuberculosis* where growth is obtained on the usual laboratory media used for acid-fast organisms, growth is also obtained in minced chick embryo tissue medium. However, in many instances growth in the tissue medium is more rapid and appears as early as 10 days following inoculation. The freshly isolated strains of *B. leprae* commonly require at least 1 week for incubation, or as long as 10 to 12 days. Growth is definite, but by no means luxuriant, the same being true for the human strains and bovine strains of *B. tuberculosis*. The avian strain of *B. tuberculosis* and the Duval and Kedrowski strains of so-called *B. leprae*, however, grow very luxuriantly in the tissue medium. The addition of glycerol to the tissue medium favors growth of our strains of *B. leprae*, but apparently does not enhance conditions for multiplication in tissue medium for the human and bovine strains of *B. tuberculosis*. Details of the method used for cultivation in chick embryo tissue medium are fully described.

Discussion

(Dr. Esmond R. Long, Chicago.) This has always seemed to me to be the most logical method to use in the cultivation of pathogenic organisms. It is a pretty rude jolt to bacteria to take them from living tissues and put them in the artificial media which we use. Moreover, in recent years we have learned that we can modify the morphology and possibly also the virulence of microörganisms by growth on different artificial media, so that it would be the most logical thing to put them in tissues where they are most likely to retain their pathogenic property. I was interested to hear that Dr. McKinley is using human tissues for his growth of acid-fast bacilli. It seems to me that is carrying logic to the most desired point.

EXPERIMENTAL EPIDEMIOLOGY OF TUBERCULOSIS. THE EFFECT OF A PRIMARY INFECTION WITH TUBERCLE BACILLI OF THE HUMAN TYPE ON CONTACT TUBERCULOSIS IN RABBITS. Max B. Lurie, Philadelphia, Pa.

Abstract. Normal rabbits exposed to tuberculous cage mates infected with the bovine bacillus acquire a respiratory or an alimentary infection that is fatal in 50 per cent of the cases. The incidence of this naturally acquired tuberculosis was 73 per cent within a year of exposure.

A large proportion of rabbits vaccinated with virulent tubercle bacilli of the human type are completely protected from natural infection for the first 6 months of the exposure. This protection wanes with further exposure and some rabbits succumb to an exogenous, naturally acquired reinfection. Both the

human tubercle bacillus of the primary infection and the bovine bacillus of reinfection may be isolated in pure culture from the same rabbit.

The vaccination reduces the incidence and mortality of the disease, changes its pathological characteristics, and retards its progress.

A method is offered whereby naturally acquired tuberculosis closely simulating the natural infection in man can be studied in a small laboratory animal.

Discussion

(Dr. E. T. Bell, Minneapolis.) This work appears to demonstrate some protection against tuberculosis of the contact type.

(Dr. Joseph D. Aronson, Philadelphia.) It appears to me that the most interesting group of animals in Dr. Lurie's experiments are those among the vaccinated rabbits which survived for a long period of time and among whom there was a high mortality from tuberculosis. Is it possible that in these vaccinated animals the tubercle bacilli are to a great extent destroyed, leaving a small number of virulent tubercle bacilli which multiply slowly, or that the virulence of the organisms increases so as to overcome the extent of vaccination?

I should like to ask Dr. Lurie whether the cultures of tubercle bacilli isolated from vaccinated rabbits show any difference in degree of virulence, as compared to cultures of tubercle bacilli isolated from the unvaccinated ones.

(Dr. Esmond R. Long, Chicago.) One important point that Dr. Lurie made clear is that in spite of vaccination, in the long run, the vaccinated animals tended to develop tuberculosis. In fact, his figures at the late period showed a larger number of animals developing tuberculosis among the vaccinated than among the unvaccinated. That might be accidental, as 30 or 40 animals may not have been a large enough series to settle the point. An important matter is to determine individual variations in susceptibility in normal animals, and Dr. Lurie at the present time is studying families of rabbits which are somewhat analogous to human families, and is trying to learn if constant variations in susceptibility occur.

Another point he made, but might have stressed more, is that when such variations to susceptibility can be established, one may infer from certain observations that this increased natural resistance can be enhanced by vaccination. Vaccination is not so much of a help to animals that have an extremely low natural resistance. So we must study the factors of natural susceptibility and resistance as part of this problem.

(Dr. Lurie, closing.) In reply to Dr. Aronson's question, I have isolated tubercle bacilli from normal animals that have acquired tuberculosis, and also from vaccinated animals that have acquired tuberculosis, and I have determined their virulence and, so far, there was no difference in the virulence of the strains, whether they originated from normal animals or vaccinated animals.

I wonder if I have the right to make the following suggestion. I feel that the reason why those 7 vaccinated animals could have been deleteriously influenced by vaccination may be due to the fact of fixation of bacilli. It is well known that sensitization results in fixation of bacilli at the portal of entry, whatever the mechanism of fixation. We also know that no matter how great the immunity that results from infection, it is always relative. In view of the fact that many bacilli are constantly absorbed, especially in the intestines, it is possible that many more bacilli will accumulate in given localities in the vaccinated than in the normal animal, as a result of the tendency of fixation of bacilli by the sensi-

tized animal. In the normal animals fewer bacilli become fixed in the same localities. In the vaccinated animals the immunity is overwhelmed by the large accumulation of bacilli at the portal of entry. The smaller numbers of bacilli present at any one time at the portal of entry of the normal animals may be destroyed by the factors of inherent resistance.

In reply to Dr. Long, I have not stressed the factors of natural resistance, but it is really very important. After all, this vaccination has only decreased the mortality by 13 per cent in the long run, although in the first 6 months the protection was great, because only half as many normal animals escaped infection. The question of natural resistance in infectious diseases is now becoming more and more important.

As to the question of Dr. Bell, we only used subcutaneous inoculation because we wanted to have a lesion that would be localized as much as possible, but even in those cases where rabbits developed a generalized infection with localization in the lung and the kidney as a result of vaccination, exogenous reinfection occurred, so that I question whether if we had vaccinated them in a different way it would have materially influenced the course of the disease.

A Factor in the Mechanism of Invasiveness by Pyogenic Bacteria. Valy Menkin, Boston, Mass.

Abstract. Trypan blue injected into an area of cutaneous inflammation induced by *Staphylococcus aureus* fails to drain readily to the tributary lymphatics if the dye is injected as early as 1 hour after the inoculation of the microörganisms.

Trypan blue introduced into an area of cutaneous inflammation induced by *Pneumococcus* Type I is retained *in situ* if the dye is injected about 6 or more hours after the inoculation of the bacteria.

When an area of cutaneous inflammation is induced by the inoculation of a culture of *Streptococcus hemolyticus*, trypan blue injected into it drains readily to the tributary lymphatics for the first 30 hours following the onset of the inflammatory reaction. If the inflammation has lasted for 45 hours or longer, the dye is fixed *in situ* and fails in most instances to reach readily the tributary lymphatics.

The rapidity of fixation of the dye is correlated by simultaneous mechanical obstruction in the form of a fibrinous network and thrombosed lymphatics, or of thrombosed lymphatics alone at the site of inflammation induced by each of the aforementioned pyogenic organisms.

Inasmuch as staphylococci, pneumococci, and streptococci disseminate from the site of their cutaneous inoculation primarily through lymphatic channels, the difference in the rapidity with which mechanical obstruction is set up in the respective inflamed areas is a factor in explaining the invasive abilities of these pyogenic organisms.

Discussion

(Dr. E. T. Bell, Minneapolis.) Dr. Menkin has done very interesting work on the fundamental phenomena in inflammation. He stresses, as most of you know, the mechanical factors in preventing the spread of organisms, and I gather that he thinks mechanical factors are much more important in the later than in the earlier stages of inflammation.

(Dr. Arnold Rich, Baltimore.) I should like to ask Dr. Menkin a question. As I understand it, he feels that the relative speed with which the lymphatics

become thrombosed is the chief factor that determines whether or not bacteria will spread from a site of infection. It is true that in the human being streptococci are often highly invasive, but in the rabbit it is almost impossible to find a streptococcus which, if injected into the skin, will spread readily through the tissues and invade the blood stream to produce a fatal septicemia. On the other hand, the Type I *Pneumococcus* is one of the most highly invasive bacteria imaginable in the rabbit. Injected into the skin, it invariably spreads to produce huge local lesions, and it invades the blood stream within several hours, the animal dying in a day or so with generalized septicemia. Now, according to Dr. Menkin, the streptococcus (which, in the rabbit, has very feeble invasive powers) does not cause early thrombosis of lymphatics in that animal, whereas the pneumococcus, which is extremely invasive, does do so. I should like to ask Dr. Menkin how he reconciles these facts with his view that thrombosis of lymphatics is the factor that prevents invasion.

(Dr. Menkin.) In answer to the question that has been raised by Dr. Rich, I should like to point out that when one introduces into the skin a substance, whatever the substance may be, whether it is inorganic or bacterial, a part of it disseminates promptly into the lymphatics and thence into the blood stream. Consequently when one inoculates a rabbit intracutaneously with *Pneumococcus* Type I, some of these microörganisms doubtless disseminate into the blood stream at least within the first 6 hours. In fact, we have in the first 6 hours obtained pneumococci by culturing the lymph obtained from the efferent lymphatic vessel. These organisms will ultimately reach the blood stream and produce a positive blood culture. Evidently those animals in which multiplication in the blood stream of pneumococci is more extensive probably succumb to the infection; but this has little to do with what is occurring at the site of inoculation, for although some cocci may have disseminated immediately after their inoculation, the infected skin area, as it develops an inflammatory reaction, will be gradually shut off, and the quicker it is circumscribed the fewer bacteria will disseminate eventually into the blood stream.

(Dr. Rich.) But did the streptococci invade the tissues and blood stream of your animals as freely as the pneumococci? Did your blood cultures and lymph cultures show a comparable dissemination?

(Dr. Menkin, closing.) Yes, indeed, streptococci disseminate readily into the tributary lymphatics from which they have been cultured. We are discussing dissemination and not virulence or resistance. Dr. Rich is evidently discussing the question of virulence and resistance, which is not the same as dissemination. In other words, if an organism reaches the blood stream very soon after its dermal inoculation, and if it happens to be extremely virulent for the rabbit, it will multiply rapidly in the circulation, causing ultimately death from septicemia, irrespective of the fact that the site of inoculation in the skin might at the time of death be completely walled off. The streptococci, on the other hand, disseminate freely into the blood stream, for there is apparently nothing that walls them off, and therefore retard their passage for the first 2 days after their cutaneous inoculation. However, the animal does not necessarily die if the particular strain of streptococci used happens to be avirulent for the rabbit. Resistance is not to be confused with dissemination, as has often been done in the literature.

THE HEART VALVES IN EXPERIMENTAL SCURVY AND IN SCURVY WITH SUPERIMPOSED INFECTION. James F. Rinehart and (by invitation) Stacy R. Mettier, San Francisco, Calif.

Abstract. In experiments designed primarily to study the reaction of the blood and blood-forming tissues of the scorbutic guinea pig to infection, routine examination of the heart revealed occasional peculiar proliferative lesions in the heart valves. This led to a more detailed study of the effect of scurvy and of scurvy combined with infection upon the heart valves, heart muscle and pericardium in the guinea pig. The diet used is a modification of that of Dahldorf and has proved quite adequate for growth and maintenance when supplemented with orange juice. Vitamins other than C are present in generous amounts and the mineral content is adequate. The infecting agent used was a hemolytic streptococcus derived from the spontaneous lymphadenitis common in the guinea pig (*B. aertrycke* was used in a small independent series of animals). The streptococcus was transmitted by intracutaneous inoculation of a pure broth culture. This produced a skin infection and infection of the regional lymph nodes. It is comparatively unusual for it to produce metastatic blood-borne lesions.

More than 90 animals were used in the study, divided into the following general groups:

1. Dietary controls — basal diet supplemented with adequate daily orange juice.
2. Acute scurvy — basal diet alone.
3. Subacute or chronic scurvy — basal diet with inadequate amounts of orange juice.
4. Dietary controls infected by intracutaneous inoculation of hemolytic streptococci.
5. Acute scurvy with superimposed streptococcus infection.
6. Subacute or chronic scurvy with superimposed infection.
7. Infection with superimposed scurvy (subacute).

The experiments were performed in four series. The results were sufficiently consistent in each series to justify the observations set forth.

Control animals show essentially normal heart valves. The normal valves possess a compact appearance with a rich, closely set, wavy, collagen fiber structure. A delicate endothelial surface layer is visible. Of 8 dietary control animals, adequate sections were obtained in 6. Of these, the valves showed a normally rich fiber structure in all. One animal showed a very mild proliferation of the endothelium overlying the insertion of one of the large chordae tendineae.

The animals on the basal diet supplemented with orange juice and experimentally infected with streptococci showed essentially normal valves in all but three instances. One animal showed an acute, necrotizing mitral valvulitis; the second an accumulation of a few polynuclear leukocytes near the base of the tricuspid valve, with some associated capillary endothelial hyperplasia. The third animal developed a uremia from an obstructed urinary tract and showed a peculiar collagen degeneration in the mitral valve. In a few other instances there were seen a meager increase in the free cells in the mitral valve and an occasional small questionable focus of edema or degeneration. The hearts of 15 animals were adequately examined in this group. No proliferative reactions were seen, such as occurred in the groups to be described.

In acute or severe chronic scurvy without infection, definite degenerative lesions were observed in the heart valves. The normally rich fibrous structures became impoverished. The valves showed thinning, fragmentation and disorganization of the regular axial arrangement of the fibers. A loss of the normal wavy contours and at times a hyaline degenerative change of the fiber substance was observed. Nine of ten hearts adequately examined in uncomplicated scurvy revealed changes of this sort. In two instances mild but definite proliferative reactions were noted at the contact area of the mitral valve. The nuclei of the stroma cells frequently showed shrunken pyknotic contours. In animals subjected to both scurvy and infection striking pathological changes were observed in considerable numbers. The findings were consistent in each of four series of experiments. The lesions observed were a combination of the degenerative effects described in scurvy with, in addition, in many instances, proliferative reactions on the part of the stroma and surface endothelial cells. Thirty-one animals were subjected to a combination of scurvy and streptococcus infection. Of these a reasonably adequate examination of the heart valves was secured in 24 animals. Practically all of these 24 animals presented recognizable degenerative changes in one or more heart valves. In addition 16 animals (66 per cent) showed moderate or marked proliferative reaction on the part of the stroma and surface endothelial cells in one or more of the heart valves. The proliferated cells present one or more large vesicular or hyperchromatic nuclei and a rather abundant dull eosinophilic or basophilic cytoplasm. At times these large cells are in intimate association with a hyaline eosinophilic material of undetermined character. The picture in the simpler proliferative lesions is in agreement with the early lesions of rheumatic endocarditis, and proliferative reactions associated with the hyaline substance bear a striking resemblance to the lesions, as seen in postmortem examination in typical verrucous rheumatic endocarditis. The proliferated cells in the experimental lesion closely resemble those in the rheumatic valve. It is emphasized that the reaction is not exudative, as in bacterial endocarditis. The proliferative reactions described in the valves occurred for the most part at the contact edges, as seen in acute rheumatic fever. In a number of instances small focal accumulations of cells were seen lying beneath the mural endocardium, within the muscle, or at the zone of attachment of the mitral valve. These reactions, essentially large cell proliferative lesions, recall the Aschoff reaction of acute rheumatic fever. These lesions differ from the accumulations of lymphocytes or of lymphocytes with a few large mononuclear cells and foci of more or less mature fibroblasts occasionally encountered in control animals or in animals with simple infection. Well defined proliferative reactions of large and, at times, multinucleated cells in the epicardial and pericardial tissues were observed in several instances, occurring both in uncomplicated scurvy and in scurvy with superimposed infection.

Discussion

(Dr. E. T. Bell, Minneapolis.) The valvular lesions demonstrated, I think, are indistinguishable from those of acute rheumatic fever.

(Dr. B. J. Clawson, Minneapolis.) I should like to compliment Dr. Rinehart on his experimental work. Those lesions which he showed on the valves correspond in every way to the lesions found in acute rheumatic fever. The hyalinized material is like that in the valve in acute rheumatic fever. I think this is the best piece of work on experimental lesions in heart valves that I have seen described.

CELLULAR REACTIONS TO MALARIA (*Plasmodium brasilianum*) IN PANAMANIAN MONKEYS. William H. Taliaferro (by invitation) and Paul R. Cannon, Chicago, Ill.

Abstract. The death and removal of malarial parasites during the course of initial infections and during immunity to superinfection can be directly correlated with the activity of the macrophages, chiefly of the spleen and liver, and to a much lesser degree of the bone marrow. The macrophages of the other tissues are involved only to a very small degree, if at all.

During the acute rise of an initial attack there is a constant, but comparatively low, death rate of parasites, which is correlated with a sluggish phagocytosis by the macrophages. The initial attack is terminated by a sudden disappearance of the forms from the blood (crisis) and is followed by a low grade infection and eventually by a latent infection in which no parasites can be found in the blood except during temporary relapses.

The disappearance of the parasites at the time of the crisis is correlated with a very striking accumulation of the parasites in the spleen and liver. In sections of the spleen the parasites can be seen to accumulate in the splenic cords, but not to pass into the venous sinuses. This concentration proceeds for about 2 days, when the accumulated parasites are suddenly ingested by the macrophages. Both the concentration and later phagocytosis mark the beginning of the acquired immunity and are observable through the remainder of the infection whenever there are enough parasites to make observations.

When immunity to superinfection is tested by injecting parasites into an animal with a latent infection, the macrophages behave as they do at the time of the crisis. Concentration in the spleen and liver begins immediately and phagocytosis takes place within less than 24 hours.

Concomitantly with the development of macrophage activity there is an increasing hyperplasia of the lymphoid elements, particularly of the spleen, the bone marrow, and sometimes the liver (mantling). The degree of lymphoid activation depends upon the severity and length of the infection. In some heavy infections it was pronounced within 48 hours, whereas in others it was only moderate after 14 days.

The hyperplasia of the lymphoid elements and the increased physiological activity of the macrophages present a striking picture of mesenchymal activation, and are in almost exact agreement with our results on the cellular basis of acquired immunity to avian malaria.

Discussion

(Dr. Paul R. Cannon, Chicago.) This work furnishes an exceptional opportunity to study the effects of an infectious agent in the tissues because of our ability to see the parasites and to determine their numbers and fate in the various organs. I should like to emphasize also that there is a striking similarity between the reactions observed and those described with bacteria. Bacteria injected into normal and immune rabbits are removed much more rapidly from the blood stream and are concentrated much more effectively in the spleen and liver of the immune animals. It seems to me that by studying the distribution and fate of malarial parasites we may get ideas not only in regard to parasitology, but also for the study of such bacterial infections as tuberculosis and syphilis, where there is also unequal localization in different organs, as affected by the immune reaction.

(Dr. E. T. Bell, Minneapolis.) I should like to ask if you were able to stain the protoplasm and chromosomes of these parasites in the tissues, and I wish you would tell us how you did it.

(Dr. James Ewing, New York City.) I was very much interested in this report on a disease which of recent years seems to have attracted less and less attention in proportion to the success of preventive medicine. In the Spanish War in 1898 I had the opportunity to observe large numbers of cases that had the aestivo-autumnal infection, and since most of these were fatal, autopsy material was abundant. In that study I was much impressed with the importance of the bone marrow as a factor in malarial infection, and was somewhat surprised to hear that the authors felt that the bone marrow is less important than the spleen and lymph nodes and liver. However, in one of your sections, the only one you showed of bone marrow, the cellular activity is very great. I found the bone marrow a most important factor in aestivo-autumnal malaria. There was a remarkable activity of phagocytosis and a great massing of parasites, extreme multiple infections in the red cells up to six or seven in one cell, and the persistence of parasites in the bone marrow when they were missing in the other organs. All these observations led me to conclude that the bone marrow has a very important influence on human aestivo-autumnal malaria. The disease in the monkey may make a difference, but I wonder if the authors have paid as much attention to the bone marrow as to the spleen and liver.

(Dr. Ralph Miller, Hanover, N. H.) I should like to ask if there was a lymphocytosis which corresponded to the hyperplasia of the lymphatic tissue of the spleen.

(Dr. Taliaferro, closing.) In regard to Dr. Bell's question concerning the staining we have been using Maximow's combination of hematoxylin and eosin-azur. With this, the chromatin of the parasite does not show up well, but the cytoplasm and pigment are beautifully clear.

In regard to Dr. Ewing's statement we have paid a great deal of attention to the bone marrow and were much surprised that the bone marrow seems so unimportant in this work. The difference between your findings and ours may be associated with the fact that you were probably dealing with terminal infections where if the parasites overwhelm the patient and the liver and spleen defenses break down, the bone marrow comes into play. We were dealing largely with animals that recovered. The very fact that you found parasites surviving in the bone marrow would indicate that phagocytosis was not going on as actively as in the spleen and liver.

In reply to Dr. Miller's question, we did get a striking lymphocytosis in some monkeys, but not in others. This was associated with an actual lymphoid hyperplasia, the extent of which depends upon the length and intensity of the infection. In a short infection only the macrophages come into play. In long infections, on the other hand, lymphoid hyperplasia in all phases may be encountered along with the macrophage activity.

THE NEUTRALIZATION OF POLIOMYELITIS VIRUS BY THE SERUM OF NORMAL ADULTS OF NASHVILLE, TENN. N. Paul Hudson and (by invitation) William Litterer, Chicago, Ill.

Abstract. The serums of 25 normal, adult white residents of Nashville, Tenn., were tested for their ability to neutralize poliomyelitis virus. Twenty-one specimens were virucidal when examined without dilution, and 16 of these neutral-

ized the virus when tested again in a further dilution of 1 in 5. An analysis of the age of the donors in relation to the results showed that those of the upper age group (30 to 44 years) had a higher proportion of neutralizing serums and that more specimens were virucidal in the arbitrarily chosen dilution of 1 in 5, than those of the lower age group (17 to 29 years).

Poliomyelitis has occurred in Nashville and in other parts of Tennessee for many years without, however, the appearance of epidemics. Our experimental results are consistent with the epidemiological features of the disease in Southern states. Before it is concluded, however, that the neutralizing property demonstrated is a specific response to exposure to the virus of poliomyelitis, or whether or not it is a manifestation of serological ripening with maturation of the individual, further observations and experimentation must be made.

The high proportion of individuals examined whose serum neutralized virus gives a basis for experimentation in the use of such serum in poliomyelitis therapy.

Discussion

(Dr. Sidney D. Kramer, Brooklyn.) Dr. Hudson, through his own results, as well as similar results collected from the literature, has shown very well that immunity to poliomyelitis is widespread in the general population. He brings up a point, however, that I should like to comment upon. He suggests, as others have recently, that the immunity as determined by the neutralization test may not be specific in type, but may be a maturation phenomenon. It might be well, until more than the inferential data that have been offered in evidence of such a notion is brought forth, to retain our present concept of immunity for which there is considerable concrete evidence. Sawyer's work on yellow fever and Morales' work on diphtheria indicate clearly that immunity to these two diseases occurs only as a result of exposure to the virus of the disease, and, in the case of yellow fever, no immunity was found in localities where this disease does not exist. In poliomyelitis the evidence is almost as striking. The low incidence of immunity in rural districts, the marked correspondence of immunity to the age distribution of the disease, and the fact that the virus has been found in normal contacts suggesting a carrier factor indicate that the presence of immunity to this disease is a result of previous exposure to the virus.

THE RELATION OF ALLERGY TO RESISTANCE IN STREPTOCOCCIC INFECTION.
B. J. Clawson, Minneapolis, Minn.

Abstract. An experimental study of the relation of allergy to resistance was made. A series of 10 animals was made hypersensitive (allergic) to streptococci. A similar series was made highly immune to streptococci without developing the allergic state.

The rate at which living streptococci were removed from the blood and liver following intravenous injections was compared in these two series and with normal animals. The height of the streptococcic agglutination titer was also compared in the three series of animals.

Fifteen minutes after injection organisms were not removed from the blood stream as rapidly from the allergic animals as from the normal animals. This suggested some harmful factor associated with the phenomenon of allergy. After 2 hours, however, a greater number of streptococci per gram of liver was killed in the allergic animals than in the normal animals. This difference was but slight.

The animals that were made immune without developing allergy, on the other hand, killed organisms in the blood stream and in the liver at a much greater rate than either the normal or the allergic animals.

The findings in the experiments suggest that the allergic state is not necessary in the process of general protective immunity to streptococci. It even seems that allergy may be harmful from the standpoint of its effect upon the phagocytic cells.

Conclusions: 1. Resistance to streptococcic infection can be developed artificially without producing a measurable amount of hypersensitiveness (allergy).

2. The state of streptococcic allergy bears no necessary relation to general resistance.

3. Allergy as related to general resistance to streptococci seems to be a useless and at times harmful concomitant phenomenon.

Discussion

(Dr. Max B. Lurie, Philadelphia.) A study of the correlation between the histological changes and the fate of tubercle bacilli cultured from different organs of the rabbit, normal rabbits as well as rabbits that have undergone a previous infection with tubercle bacilli, showed that the capacity of the tissues to destroy the reinfecting organism was related not so much to the intensity of inflammation as to the degree of acceleration of the inflammatory reaction. The greatest amount of destruction of tubercle bacilli took place in the absence of any but negligible inflammation; that is, if the animal had a very extensive primary lesion and it was reinfected, that animal destroyed the tubercle bacilli immediately, and in the organs, except for rare minute mononuclear nodules, there was practically no inflammation at the end of 24 hours. An animal with little or no residual primary lesion, which reacted to reinfection with intense inflammation, did not destroy the tubercle bacilli as rapidly as did the animal that reacted with little inflammation.

(Dr. Paul R. Cannon, Chicago.) Has Dr. Clawson cultured the liver and spleen and various organs at as early a period as 5 minutes after infection? In some of our studies we have observed in injecting living organisms intravenously into normal and immune animals that within 5 minutes there are many more organisms per gram of tissue in the spleen and liver of the immune than of the normal animal. In similar experiments an hour afterwards there is just the reverse, as Dr. Clawson has shown. It seems to me this finding emphasizes even more strikingly the ability of the immune tissues to concentrate and also to destroy organisms, because, for example, if an immune spleen contains three times as many organisms at the end of 5 minutes as the normal animal, but at the end of 30 minutes has only one-third as many viable organisms, the killing power of the immune spleen would be nine times that of the normal. I wonder whether or not Dr. Clawson has observed this phenomenon.

(Dr. Reuben L. Kahn, Ann Arbor.) I am very much interested in Dr. Clawson's work because we have been investigating problems of a similar nature during the past 2 years. While I do not question Dr. Clawson's results, I am inclined to question if rabbits should be classified as immune or allergic, depending on whether they were injected intravenously or in the tissues. We believe that the difference in the degree of allergy of the cutaneously and intravenously injected animals is quantitative and not qualitative, and it appears to us that an analysis of the data shown by Dr. Clawson proves this view. We believe, too,

that one can lay down a law that a protein, whether it be bacterial or any other type, when introduced in sufficient quantity into the tissues of an animal, will produce a certain degree of allergy.

(Dr. Clawson, closing.) Dr. Lurie's work which has recently been published seems to agree with my findings on streptococci.

In regard to Dr. Cannon's question — yes, I have tested the number of organisms in the liver, spleen and bone marrow at different times and have found, as you did, that at first a greater number of organisms will be found in the liver in the immune animals than in the allergic animals. With this strain of streptococci all the organisms will disappear from the blood stream in something like 30 minutes. If at that time the liver, spleen and bone marrow are cultured, we shall find a greater number of organisms in the immune animals, but it decreases more rapidly also in the immune animals. I used the 2 hour period because it seemed to me a period that would differentiate more sharply between the two kinds of immune reactions.

In regard to Dr. Kahn's question of immunity and allergy, or the use of the term "immune" and "allergic" animals, I think the criticism is well taken. Of course I mean the animals that were made immune without a measurable amount of allergy, and the animals that were made allergic with a low degree of immunity. Those are the two kinds of animals I was using and my results did show that my allergic animals had some protection. I do not know how to produce allergy without producing some immunity. I do think, however, that a high degree of immunity can be produced by streptococci without producing allergy. The method I used to measure my allergy was the delayed tissue reaction. I injected a measured amount of streptococci subcutaneously. With the animals previously injected intravenously, I got even less allergy, less tissue response than I did in the normal animals. In regard to allergy being harmful, I think most workers in tuberculosis would be very happy if they could eliminate the allergic factor in the pathogenesis of a tuberculous lesion in the lung. Allergy and immunity can be separated. For instance, you cannot transfer allergy passively, while immunity can be transferred passively.

INHERENT FACTORS IN RESISTANCE AND SUSCEPTIBILITY TO INFECTIOUS DISEASES. Leslie T. Webster, New York City.

Abstract. Selective breeding experiments were carried out on several strains of mice to determine the possibility of segregating lines relatively susceptible or resistant to a given infection. Care was taken to ensure that the test animals had had no previous exposure to the specific agents and that they contracted a natural rather than an artificial infection. From the Rockefeller Institute hybrid strain, 37 per cent susceptible to *B. enteritidis* mouse typhoid, lines 85 per cent and lines 15 per cent susceptible respectively were selected. The former were descendants of individuals highly susceptible, the latter of individuals relatively resistant. From white-face and black-and-tan strains, lines 90 per cent and lines 95 per cent susceptible were developed in a similar manner. The selected mice reacted consistently when exposed to spontaneous herd infection. Cross and back-cross breeding of susceptibles with resistants gave results indicating that resistance factors are dominant and not sex-linked. Selected mice, with the exception of the white-face strain, were of average weight and fertility. Resistant mice were heavier but not more fertile than susceptible mice. Tissues of resistant mice, not only at the natural portal of entry but throughout the

body, appeared less sensitive to *B. enteritidis* than those of susceptible mice, suggesting a general rather than local influence of the inherent factors. Finally, the several lines were tested for their relative resistance to nasal instillation of *Pasteurella avicidia*, *B. friedlaenderi*, pneumococci, and louping-ill virus. The susceptible white-face line proved highly susceptible to all, the Rockefeller Institute susceptible lines relatively susceptible to the respiratory bacteria and resistant to the virus, the black-and-tan resistant to the bacteria and susceptible to the virus, and the Rockefeller Institute resistant lines resistant to the bacteria and susceptible to the virus, thus indicating that genetic factors concerned with susceptibility or resistance to infection can operate consistently against a number of, but not necessarily all, harmful agents.

Discussion

(Dr. H. G. Wells, Chicago.) This paper is of great importance from the standpoint of the man doing investigative work in infectious disease, as it brings out strikingly the fact that experiments carried out on animals of unknown pedigree give results that are likely to lead to error. I want to call attention to how this coincides with the work of a Dutch investigator, Hagedorn-Le Brand, who published his results in a journal little known to medical men, and therefore they have not received as much attention as they deserved. In brief, his experience was something like this: a strain of mice was picked up in the United States and another strain in Japan, and they were taken to Java for some work on heredity. After a few crossings had been accomplished, an epidemic infection of staphylococcus origin broke out in the stock, and when it was all over and there were no further deaths among the animals the breeder began to make a charting of his results, which brought out an almost perfect Mendelian result. All of the Japanese stock were dead; not one of the American stock was dead, and of the various hybrids in the stock part were dead and part alive, in almost exactly the Mendelian expectation. This illustrates the fact again that susceptibility behaves essentially as a recessive.

THE DIFFERENTIAL STAINING OF LIVING AND DEAD BACTERIA. Frederick P. Gay and (by invitation) Ada R. Clark, New York City.

Abstract. The action of dye stuffs on bacteria is of importance not simply as a means of their identification but in such fundamental problems as investigation of bacterial structure and physiology, the mode of action of disinfectants and the possibilities of dye therapy, and finally on the protoplasmic changes that underlie life and death processes. The authors have made an extensive study of the Proca-Kayser combination staining method, which in their hands has given extraordinarily great accuracy in the identification of dead bacteria, as contrasted with living bacteria. The only other dye stuff systematically investigated is neutral red, which, properly speaking, is a vital stain rather than a stain that differentiates living from dead organisms and which bears on the matter of destruction of bacteria within phagocytes rather than outside them.

A large list of bacteria has been investigated and for comparison yeast cells and nucleated red blood cells stained by the Proca method and by neutral red. Death of bacteria produced in many different fashions has been found to give uniformly consistent results with the Proca stain, which, subject to natural limitations of technique, has been found invariably indicative of life or death.

Reference will be made to studies of nucleated red blood cells which offer certain analogies to the staining of bacteria. Various forms of hemolysis have been studied here and fruitless attempts made to show demonstrable changes in the staining reaction of specifically sensitized cells. The contrasting effects of death both of bacteria and of nucleated red cells within and without phagocytes will be referred to.

Discussion

(Dr. William H. Taliaferro, Chicago.) I should like to ask if Dr. Gay has tried this on protozoan cysts.

(Dr. Gay.) No, we have not. The only very extensive studies that we have undertaken are studies of the nucleated red blood cells under various conditions that cause hemolysis, and I may say that the same change takes place, for the nuclei of such red blood cells stain blue under normal conditions, and the moment these cells are hemolyzed, the nuclei swell and stain red.

CHANGES THAT MAY BE INDUCED IN THE BEHAVIOR OF *B. Typhosus*, WITH REFERENCE TO THE CRITERIA FOR IDENTIFICATION OF THE SPECIES. Ruth Gilbert and (by invitation) Marion B. Coleman, Albany, N. Y.

Abstract. The properties of strains of *B. typhosus* that have been altered after remaining in media containing immune serum have been correlated with those of cultures that are occasionally isolated from fecal specimens. The cultures from both sources mentioned differ from typical strains of *B. typhosus* in that they produce indol, are not agglutinated in typhoid antisera, are non-motile, and ferment rhamnose. Precipitation tests have demonstrated a serological relation between these two types of cultures, that is, the inagglutinable variants of *B. typhosus* and certain of the strains having similar characteristics which have been isolated from the feces of persons convalescent from typhoid fever, from those suspected of being or known to be carriers of *B. typhosus*, and from patients having enteritis of unknown etiology. These findings suggest that the criteria for the identification of *B. typhosus* may need to be revised.

Discussion

(Dr. Leland W. Parr, Washington.) In the isolation of these organisms directly from the feces, or in the culture media, was it your experience ever to observe mucoid encapsulated forms?

(Miss Coleman.) No, mucoid encapsulated forms of the variant have not as yet been found. Encapsulated strains of *B. typhosus* are occasionally isolated, however.

STENOSIS OF PULMONARY CONUS AT LOWER BULBAR ORIFICE, WITH INTERVENTRICULAR SEPTUM ENTIRE (WITH TWO ILLUSTRATIVE CASES). Maude E. Abbott and (by invitation) W. W. Eakin, Montreal, Canada.

Abstract. The rarity of this combination is pointed out and this and other points of interest discussed. In Case 1, a cyanotic boy aged 12 years, the fetal passages were all closed and the myocardium of the greatly hypertrophied right ventricle was the site of an extraordinary degree of fibrosis and localized obliterative sclerosis of the coronaries. In Case 2 the foramen ovale was widely patent and the constriction was the site of extensive vegetations and of a tag 5 cm. long,

which projected free from the pulmonary artery (*Streptococcus viridans* infection).

Only 2 cases have been found in the literature showing this type of stenosis with *closed ventricular septum*, those of Lafitte and Jackson Clarke.

PHOSPHORUS AND ALCOHOLIC CIRRHOSIS. Frank B. Mallory, Boston, Mass.

Abstract. Alcoholic cirrhosis is characterized by the presence of an acidophilic hyaline network or reticulum in the cytoplasm of liver cells. Many or few cells are affected at a given time, depending on the activity of the degenerative process. The reticulum is colored blue by the Macallum and Fiske-Subbarow methods for phosphates.

Chronic poisoning with phosphorus readily produces in rabbits and guinea pigs a cirrhosis that is characterized by a similar acidophilic reticulum in the liver cells. The dose required ranges from a third to a half of a milligram of phosphorus to the kilogram of animal weight. It is given daily by mouth, dissolved in oil of sweet almonds. A minimum of 4½ months is required. The reticulum stains microchemically like that in alcoholic cirrhosis.

Phosphorus given as a remedy for rickets and to promote callus formation may explain the rare instances of alcoholic cirrhosis in children. For its frequent occurrence in adults and for its evident close relation to excessive indulgence in alcoholic beverages, some other source is demanded. But one suggests itself.

Phosphorus is often present in iron ores and thus gets into pig and cast iron and into the iron and steel vessels and containers made from them. It exists as a phosphide and as an alloy of iron. Disintegration of iron by acids in liquors and alcohol may set free phosphorus from the alloy. It would be preserved in water and especially in alcohol just as it is in oils.

Phosphorus is driven off from solutions containing it by a temperature of 30 to 40° C. It unites with the silver of photographic printing paper and if in sufficient quantity, colors it brown to black. Hydrogen sulphide acts in the same way. The sulphide and phosphide can be differentiated in the following way. Decolorize the paper in a solution of potassium permanganate acidulated with sulphuric acid. After washing in water place in the Fiske-Subbarow solution for 5 to 10 minutes. If phosphorus was present in the fluid, it forms silver phosphide in the paper and then, changed to a phosphate, turns blue; otherwise the paper remains white. Treat with hypo to remove unchanged silver salts, then wash thoroughly in water and dry.

By this method phosphorus has been demonstrated in cast iron and in the tin plate of a tomato can after they had been dissolved in dilute hydrochloric acid.

PHLEBOSCLEROSIS OF THE HEPATIC VEINS, AS ASSOCIATED WITH CHRONIC PASSIVE CONGESTION OF THE LIVER AND CARDIAC CIRRHOSIS. Eli Moschcowitz, New York, N. Y.

Abstract. Eight cases of sclerosis of the hepatic veins associated with hypertension of the pulmonary circuit, due to various causes, are reported. The lesion apparently is quite common. In all cases the lesions of hypertension of the pulmonary circuit previously described were present, namely, arteriosclerosis of the pulmonary vessels, dilatation and fibrosis of the pulmonary capillaries. Sclerosis of the hepatic veins is only present when a condition causing increased pressure in the hepatic veins can be predicated, the result in every instance of

hypertension of the pulmonary circuit with right heart failure. It is always associated with passive venous congestion of the liver with and without cardiac cirrhosis. The lesion consists in dilatation of the hepatic veins with thickening of both intima and media and proliferation of the elastic fibers, and is interpreted as compensatory to the increased intravenous pressure. Cardiac cirrhosis is an accompaniment of sclerosis of the hepatic veins, and is interpreted as a capillary sclerosis consequent to the increased pressure in the central veins. A narrow zone of cirrhosis around the vena cava and larger hepatic veins, apparently the direct result of pressure, is described as a usual accompaniment of this lesion.

SOME UNUSUAL SOURCES OF HEMORRHAGE INTO THE GASTRO-INTESTINAL TRACT. B. Earl Clarke, Providence, R. I.

Abstract. A report of autopsy findings in four patients dying from hemorrhage into the gastro-intestinal tract is presented. In no case was the source of hemorrhage diagnosed clinically. In one a primary malignant melanoma of the small intestine was found. The second had an enormous abscess of the liver which communicated with the gall-bladder. The hemorrhage occurred into the abscess from which the blood passed into the gall-bladder and through the cystic and common bile ducts into the duodenum. In the third case there had apparently been an old hemorrhagic pancreatitis with pseudocyst formation. The stomach and transverse colon were firmly adherent to the walls of this pseudocyst. Hemorrhage had occurred into the cyst and from here broken through into both the stomach and the transverse colon. The last case presented an old fibrotic pancreatitis and pancreatic calculi. The stomach was adherent to the pancreas. A sharp calculus had penetrated the stomach wall. Hemorrhage occurred into the stomach at this point of penetration.

THE PRODUCTION OF PERSISTENT HYPERTENSION IN DOGS. Harry Goldblatt and (by invitation) James Lynch, Ramon F. Hanzal and Ward W. Summerville, Cleveland, O.

Abstract. In ten dogs, by the carotid loop method of Van Leersum, systolic blood pressure was determined daily for at least 2 months before, and for from 3 to 9 months after, the constriction of both renal arteries by means of a special clamp devised for the purpose. The clamp permitted the degree of constriction of the vessel to be varied. In some of the dogs the constriction was made great from the beginning; in others it was made moderate at first and subsequently increased. Constriction of one renal artery was followed by a moderate or slight rise of blood pressure which tended soon to return toward the normal level. Following the production of bilateral renal ischemia the blood pressure rose to a varying degree in all of the animals. During a variable period following the constriction of the second vessel very high values were common. No attempt was made in this series of animals to remove the accessory circulation through the capsule of the kidney. Probably due to this accessory circulation the pressure tended to decrease in most of the animals, but in all it has remained elevated well above the normal.

In two dogs, in which the clamping of both arteries was made almost complete from the start, the rise of blood pressure that followed was accompanied by the development of uremia, which proved fatal in a few days. In these dogs urea nitrogen, total non-protein nitrogen, creatinin, and methylguanidin in the

blood kept increasing and the urea clearance and output of phenolsulphonephthalein kept decreasing until death. In the remaining eight animals which have survived for many months the only function test that has indicated some renal damage in a few of the animals is the urea clearance. In one dog that has had persistent hypertension for 9 months following the constriction of the renal arteries the urea clearance has been consistently reduced to about 50 per cent of its own mean normal value. In the remaining animals urea clearance showed less reduction or practically no change from the normal.

In one dog the splenic artery and both femoral arteries were greatly constricted some time before the clamps were applied to the renal arteries, but no rise of blood pressure occurred until after the renal arteries had been constricted.

In one dog the right suprarenal body was removed, the left suprarenal body was denervated and its medulla mechanically destroyed, and the left major and minor splanchnic nerves were sectioned. The blood pressure of this animal showed no significant change until after the renal arteries were constricted, when a rise promptly occurred.

Most of the animals are still alive. The examination of the kidneys of 1 of the animals that died accidentally indicates that constriction of the main renal artery can induce significant changes in the vessels of the ischemic kidney. The changes in the vessels of the kidney and of other tissues of the body are being studied.

These experiments indicate that, in dogs at least, ischemia localized to the kidneys is a sufficient condition for the production of hypertension of a type that resembles that which is associated with arteriolar nephrosclerosis in man.

Discussion

(Dr. E. B. Krumbhaar, Philadelphia.) I should like to know if there is any evidence of anemia.

(Dr. E. T. Bell, Minneapolis.) It is rather surprising that there was no more trouble with collateral circulation by clamping these arteries. When the veins are treated in this way an enormous collateral circulation develops very soon, which restores the circulation of the kidney. What is the effect if these arteries are clamped completely at first? It is a common teaching that removal of both kidneys is not followed by hypertension. Most investigators seem to think that taking out both kidneys does not cause hypertension. One idea of the fundamental mechanism is that there is first an anemia of the kidney, and then a reflex elevation of the blood pressure.

(Dr. F. W. Hartman, Detroit.) We have obtained somewhat similar results to those reported by trying deep X-ray over one or both kidneys. The kidneys in the experiments directed toward the production of hypertension are raised through the abdominal wall, and a lead plate is introduced between the kidney and the body of the dog, and then the kidney is exposed to very heavy doses of X-ray. These experiments have been reported in the literature for some time, and we got a persistent hypertension, such as Dr. Goldblatt has described. The hypertension does not occur, however, when only one kidney is treated. If one kidney is allowed to remain normal we have never yet seen appreciable and persistent hypertension, and I think that many of Dr. Goldblatt's experiments suggest the same thing, that when he only clamped one kidney there was very little, if any, persistent hypertension. That appeared from his charts.

Another angle here is that there is very little correlation between the kidney

function and the hypertension. All of these dogs treated with X-ray died eventually of kidney insufficiency but the hypertension, both diastolic and systolic, occurred before the terminal stage. In fact, the blood pressure nearly always fell in the terminal stages. The animal nearly always has a poor appetite, eats very little, begins to lose weight, and then the hypertension nearly always falls.

As to the methods of taking the blood pressure, we tried the cuff method, as Dr. Goldblatt mentioned, but in most of our dogs we found these cuffs ulcerated through and broke down as the hypertension reached the maximum, and we lost several of our best hypertension dogs from this ulceration and hemorrhage, so that I do not think this method, at least in our work, turned out very well. We used a cuff on the dog's legs similar to the ordinary mercury manometer, also maximum and minimum mercury manometers, and direct blood pressure readings were obtained. Our normals in dogs were a little lower than those recorded by Dr. Goldblatt, from 125 to 130, and I should like to ask him about the training of his animals — how they were handled in getting them in and out of the cages. We decided that blood pressure readings were of very little value unless the dogs had gone through a long period of training and were perfectly coöperative in that they allowed themselves to be lifted out of their cages, taken into the laboratory and laid down on a warm blanket, covered, and then kept perfectly still during the observation of the blood pressure. If there is any break in that technique, or if they shiver, or move on the table, the readings are absolutely worthless, in our experience.

The other thing I should like to ask about is whether there are corresponding changes in the vascular system, particularly in the heart. Was there any hypertrophy of the heart? We found in our group of animals we were able to produce heart-weight body-weight ratios practically double the normal, and the hypertrophy was readily demonstrated with a six-foot cardiac plate. I think that would be worth while to have confirmed in these experiments.

As to the eyegrounds, we also got extensive exudation which was readily demonstrated.

(Dr. Bell.) I think the cuff method gives higher readings on the normal, but it should be of comparative significance when hypertension is produced.

(Dr. Goldblatt, closing.) In answer to Dr. Krumbhaar's question we have not at the present time studied the blood; that is part of the program planned but it has not yet been done.

In answer to Dr. Bell it has been the observation of every physiologist that in acute experiments clamping of both renal arteries causes no significant change in the blood pressure. However, continued determination of the blood pressure of such animals for several days, until death, has not hitherto been carried out. In our experiments when the constriction of both renal arteries was very great, amounting to complete clamping, in so far as the blood flow in the kidneys is concerned, the blood pressure did rise and remained at very high levels until death. In such animals uremia accompanied the rise of blood pressure and proved fatal. The functional changes in our dogs that survived for a long time were less severe than in Dr. Hartman's animals.

In answer to Dr. Hartman, — I am very familiar with his experiments and with those of other investigators interested in experimental production of hypertension. None of the experiments hitherto reported used the method we have just described and which limits the possible cause of at least one type of hypertension to renal ischemia alone. On this account I did not take the time to refer to all the experiments that have been performed on the production of hyper-

tension in animals. In his experiments Dr. Hartman produced severe generalized damage to the kidney by means of roentgen rays. He was not dealing with the exclusive effects of renal ischemia. In some of our animals, after the constriction of one renal artery, there was a rise of blood pressure which did not persist unless the other artery was also constricted. This was to be anticipated if renal ischemia is to be considered the exclusive cause of this type of hypertension. This is in keeping with the knowledge we have of so-called vascular hypertension in man.

I am pleased to have the opportunity to say something about the method used for the determination of blood pressure. The animal was removed from its cage by the same assistant and carried into the room where the testing was done. After a period of rest in the box the observations were made. Ten observations of systolic blood pressure were made at one sitting every day. The mean of these 10 observations is recorded as the daily value in the charts which you have just seen. By taking the blood pressure immediately after the dog was put into the box higher values could have been obtained, but we recorded the 10 values only after a fairly uniform level had been reached. The figures are therefore probably low rather than high.

We have never observed ulceration of the carotid loop after the surgical incisions healed completely and observations of blood pressure were started. In one dog which we have observed at intervals for over 5 years, and which has had a normal blood pressure during the greater part of that time, the loop is still quite intact. Recently we clamped the renal arteries of this dog; the blood pressure has risen and the loop continues to be normal.

About the lower values for normal blood pressure in Dr. Hartman's animals I have little to say except that it is probably explained by the difference of the methods used and the site at which the pressures were taken. I do not consider this difference of significance in this connection as long as the same method is used throughout the experimental period. Since the change in the level of blood pressure and not the absolute value is the significant thing in these experiments, the result should be the same no matter by what method the blood pressure is determined.

In the beginning, during the control period, some of the animals were nervous and this perhaps raised the level of the normal value. I indicated in the charts that there was a tendency during the 2 or more months of the control period for the blood pressure to fall moderately. By the time the clamps were applied the animals had become completely accustomed to the observer so that the factor of nervousness played no part in the striking elevation of blood pressure which followed the constriction of the renal arteries.

About the changes elsewhere in the body, that is, the appearance of the vessels in other tissues and a change in the size of the heart, we have as yet little to say. We have been taking roentgenograms of the chest, and in the dog that has had persistent hypertension for 9 months following the clamping of the renal arteries there is some indication of hypertrophy of the heart. I do not believe that one can interpret the roentgenographic silhouette in quantitative terms as far as cardiac hypertrophy is concerned. This will be done best at autopsy. At the present time the dogs are all alive, except those in which both renal arteries were almost completely clamped at an interval of only a few days and which survived for too short a period to permit of any significant cardiac hypertrophy. This phase of the study is being continued in collaboration with my colleague, Dr. Alan R. Moritz.

BENIGN EPITHELIAL INVASION. William Boyd, Winnipeg, Canada.

Abstract. Epithelial invasion of deeper tissues is not necessarily malignant. The most marked examples of extensive epithelial invasion of a benign character are seen in the gall-bladder in cholecystitis glandularis proliferans. A case is described in which there is a possible change from a benign to a malignant condition. Benign epithelial invasion occurring in the stomach, uterus and Fallopian tube is also discussed.

Discussion

(Dr. E. T. Bell, Minneapolis.) I should like to ask if Dr. Boyd thinks adenomyoma of the uterus is of this type, or does he think that it is a congenital condition?

(Dr. F. W. Hartman, Detroit.) I have a specimen of a typical papillary adenocarcinoma arising in this condition which I will be glad to send Dr. Boyd.

(Dr. George Baehr, New York City.) I should like to ask if Dr. Boyd considers the crypts of Luschka in the gall-bladder an abnormality, or part of the normal histology of the organ.

(Dr. Boyd, closing.) I do consider them as abnormal, that is to say, I do not believe we ever find them in a perfectly normal gall-bladder. All those gall-bladders in which they are found show recent or old inflammation.

In regard to the question concerning adenomyoma, I do not imagine there is any direct relation between the two conditions. I imagine the adenomyoma is an entirely different process.

THE ANGLE OF THE MITOTIC SPINDLES IN MALIGNANT CELLS. Shields Warren, Boston, Mass.

Abstract. Measurements of the angle included at the centrosome by the outer fibrils of the mitotic spindle indicate that these angles may be fairly constant for different types of malignant cells. Measurements were made with the eyepiece goniometer and also through direct measurement of enlarged photomicrographs. It is necessary to be sure that the two apices of the spindle lie in the same plane, as rotation would give a false widening of the angle.

Measurements were made in 15 malignant tumors: 6 carcinomas, 4 fibrosarcomas, 2 osteogenic sarcomas, 1 melanoma, 1 glioblastoma, and 1 Ewing's tumor. The mean values obtained for the angles were: carcinoma 91°, melanoma 56°, fibrosarcoma 72° for narrow angles and 108° for wide angles, osteogenic sarcoma 69°, and Ewing's tumor 88°.

Discussion

(Dr. Stanley P. Reimann, Philadelphia.) I should like to ask Dr. Warren if he has any data on the mitotic angles in normal growing tissue, regenerating tissue, or in developing fertilized ova.

(Dr. Warren, closing.) I am working on this at the present time. I have a scattering of measurements, rather too few to say anything about for granulation tissue, and there, too, there seems to be a fairly consistent narrow angle, around 60°. I have a number of measurements from normal lymph nodes that show a range of 30° to 45°, centering about 43°.

A Theory of Pigmented Moles. Their Relation to the Evolution of Hair Follicles. George F. Laidlaw and (by invitation) Margaret R. Murray, New York, N. Y.

Abstract. Pigmented moles of human skin follow a peculiar pattern. Usually they are elevated above the general surface. There is a local accumulation of pigment. In the corium there are solid cords and clusters of nevus cells which are associated intimately with the nerves of the skin (Masson, Stout, Foot, Laidlaw). The nerves run in cords and clusters of nevus cells; here and there a nerve terminates in delicate branches which are applied to one or more nevus cells after the manner of Merkel-Ranvier tactile cells.

The most striking aspects of this pattern are two in number. First, it does not resemble anything known in normal mammalian skin. Secondly, it is a faithful reproduction of the pigmented, elevated and innervated tactile spots of the amphibia and reptiles. In the course of evolution the pigmented tactile spots of the amphibia and reptiles were replaced in mammals by hair follicles and by mammalian tactile corpuscles. The pigmented, hairy mole appears to be a link or transition from pigmented tactile organs of the amphibian-reptilian type to hairy tactile organs of the mammalian type. The pigmented, hairy mole is part mammalian and part reptilian. In its hair follicles it is mammalian; in its pigmentation, elevation and the groups of innervated nevus cells in the corium it follows the amphibian-reptilian pattern.

This evolutionary hypothesis offers an explanation of several hitherto obscure features of pigmented moles. It explains the peculiar and constant association of a pigmented elevation of the skin with hair follicles. It explains Unna's *Abtropfung* as a recapitulation of the formation of a reptilian tactile spot, in which tactile epithelia from the basal layer of the epidermis sink down into the corium, separate from the epidermis, and form connections with nerve fibers. It confirms the probability of Masson's view that nevus cells are a mingling of cells from the epidermis with Schwann cells from the nerve fibers. It explains the curious profusion of tactile corpuscles in pigmented moles of the scalp where normally no tactile corpuscles are found; for hair follicles and mammalian tactile corpuscles are parallel evolutionary products of the reptilian tactile spots (L. Plate). Finally it explains why pigmented moles are rare in hairy mammals. Their skin has specialized far beyond human skin in the production of hair. Tested by mammalian standards, human skin is a fetal skin (Bolk, Keith). In its relative absence of hair it is closer to the ancestral reptilian skin and consequently, as in its pigmented moles, it bears more vestiges of former amphibian-reptilian life.

Vascular nevi may be explained as vestiges of the rich capillary plexus of an amphibian skin, introduced at the stage when man's ancestors, the most primitive amphibia, breathed through the skin. Such a capillary plexus may be seen to-day in the skin of the lungless salamanders, the modern representatives of these first land vertebrates.

Discussion

(Dr. Nathan Chandler Foot, New York City.) I think we have to congratulate Dr. Laidlaw on the completeness of everything that he has done in this connection. The chief objection to our work with silver impregnation at the present time has been that it has been incomplete. We have seen a nerve here, and an end organ there, but we have seldom been able to link up the entire picture.

Dr. Laidlaw's remarkable method has done this, so that I do not think anybody can take exception to his pictures. Last year I sent some specimens of silver impregnation to Professor Miescher, who has been the chief contemporary exponent of the epidermoid origin of melanoma; his impression was immediately that the impregnation was incomplete, and his criticism was just. I think if Dr. Laidlaw would send him some of his impregnations there would be very little come-back. Dr. Laidlaw's work is not only complete in respect to the method, but in respect to the fact that he has brought in comparative anatomy to solve the problem, and I can bear testimony to the fact that we often find associated in the same nevus vascular and pigmented nevi, which further bears out the reptilian analogy.

(Dr. E. T. Bell, Minneapolis.) Part of the difficulty of the ordinary pathologist is that he is not able to stain things so beautifully as Dr. Laidlaw does. When we try to stain neurites and axones we get collagen and recticulin and a lot of other things. I should like to ask Dr. Laidlaw to tell us how he uses the silver stain, if this can be done simply.

(Dr. Laidlaw, closing.) The technique is very simple. These sections were stained with our 2 minute technique, based on the Gros-Bielschowsky. Tissue is fixed in neutral formalin. Frozen sections are put in 40 per cent silver nitrate for 2 minutes, then without rinsing placed in 5 per cent formalin for 2 minutes, then without rinsing placed in 5 per cent ammoniacal silver for 2 minutes, and it is done.

THE MOBILIZATION AND EXCRETION OF MELANIN IN NORMAL AND PATHOLOGICAL CONDITIONS. Victor C. Jacobsen and (by invitation) G. H. Klinck, Jr., Albany, N. Y.

Abstract. The normal distribution of melanin in the human is confined to the skin, the pigment layer of the retina, the ciliary body and the choroid, except for its presence in certain parts of the central nervous system (Bloch). Increase in the amount of melanin in these locations occurs in various pathological conditions, being especially pronounced in the malignant melanomas. The isolation of melanin in a pure state is apparently impossible at present because of its relative insolubility *in vitro* without the aid of strong acid or alkali. It must be soluble in certain of the body fluids because it or its precursor, melanogen, colors the urine in many cases of melanoma, and while it is phagocyted by various endothelial cells it has rarely, if ever, been detected in particulate form in the cells of the circulating blood. Since melanin is a constant component of many cells of the body, it follows that the pigment must be disposed of in some way when melanophores die. Also, if this be true, there is much more melanin to be disposed of in conditions of increased melanosis. If the excretion of melanin is interfered with it should be found retained in the body, especially in organs likely to have excretory powers.

In order to determine the manner of disposition of melanin normally and in diseased conditions we have studied by special methods tissues from the following sources: old persons, both blondes and brunettes, adult negroes, individuals with Addison's disease, those with benign and malignant melanoma, and about 400 white mice, each bearing a melanoma derived from one originally discovered by Harding and Passey of Guy's Hospital in 1925, and obtained by us from Sugiura in 1931.

In cases of pathological increase of melanin in the human, such as in Addison's

disease or melanomatosis, the kidneys in all instances contained much melanin in the epithelium of Henle's loops and collecting tubules, and frequently as well in the reticulo-endothelial cells of the liver, spleen, and lymph nodes. Melanin granules were often present in renal casts and one diagnosis of Addison's disease was made partly on the basis of such a finding. In the adult constipated negro melanin was regularly found in small amounts in these same sites in the kidney. Also the kidneys of old people who died of severe wasting disease showed similar findings. White mice harboring melanomas also revealed this distribution of the pigment. In melanosis coli the pigment in phagocytes in the colonic mucosa seems to be true melanin and occurs only in very constipated people.

The melanophores, or cells that can only carry pigment and not produce it, are of several types, among them being (1) macrophages, (2) endothelial cells, and (3) fibroblasts. The main paths of excretion are the kidneys and the intestinal tract, although the skin itself by desquamation doubtless releases much melanin from its own cells. The argyrophilia of melanin after thorough extraction with lipoid solvents suggests the best method at present for demonstrating melanin, and Foot's silver bromuration method has been used considerably in this study. The dopa reaction is invaluable in differentiating melanophores from melanoblasts.

The pigment in the zona reticularis of the adrenal appears to be melanin and it is suggested that the pigment is adsorbed by the epithelium after its release by the sympathetic cells of the contiguous adrenal medulla. The pigment of heart muscle is not melanin, according to our present criteria. These studies show that whenever a pigment can reasonably be assumed to be melanin its origin from cells of neuroectodermal origin is quite definitely indicated. Hence, we feel in line with Masson's dictum that melanotic tumors are of neurogenic derivation; the time has come to state unequivocally that melanin itself, no matter where it is found, is always of neurogenic origin.

RENAL LESIONS ASSOCIATED WITH MULTIPLE MYELOMAS. E. T. Bell, Minneapolis, Minn.

Abstract. Proteinuria occurs in the great majority of instances of multiple myeloma, and renal insufficiency is frequently demonstrable in the advanced stages of this disease.

Seventy-nine reports from the literature are reviewed in which the author gave information concerning blood pressure, renal function, or structural alterations in the kidneys, and 11 new cases are reported in which the histological changes in the kidneys are described.

In 4 cases no protein was found in the urine, and in 8 cases serum protein was demonstrated in the absence of Bence-Jones protein. In 60 of 74 cases, 81 per cent, in which a test was made, Bence-Jones protein was found in the urine.

In some instances structural changes in the kidneys are caused by arteriosclerosis, in others, by pyelonephritis resulting from compression of the spinal cord or prostatic hypertrophy. Renal insufficiency may be caused by lesions of these types.

The only direct effect of multiple myeloma on the kidneys is the formation of casts of Bence-Jones protein which obstruct the tubules and cause tubular atrophy. When a large number of tubules are obstructed extensive atrophy of the cortex and renal insufficiency ensue. There is no evidence that Bence-Jones protein injures either tubules or glomeruli. Cortical atrophy is due to tubular

obstruction by casts and should not be interpreted as a nephrotic contracted kidney.

In one instance renal insufficiency was apparently caused by the accumulation of a highly concentrated protein solution in the glomerular capillaries.

Discussion

(Dr. Victor C. Jacobsen, Albany.) In 1917 I reported what was regarded as the first case of multiple myeloma with Bence-Jones protein in the blood serum. It was a case of a Chinese, 60 years of age, who had typical multiple myelomas, with Bence-Jones protein in the urine. In inactivating his serum for the Wassermann test a tremendous precipitation occurred, and further analysis showed he had 7.6 per cent of the Bence-Jones protein in his blood serum. At autopsy the tumors were plasma cell myelomas. He also had very small, arteriosclerotic, granular kidneys. The Bence-Jones protein was largely dammed back in the blood stream. Since that time Bence-Jones protein has been found in the blood serum in small amounts in hypertension and in other non-neoplastic conditions, and we are beginning to know more about it. I should like to make one plea, and that is for the use of the term Bence-Jones protein. It is a protein and hence should not be spoken of as Bence-Jones "bodies," and editors should coöperate in eliminating the latter term from future literature.

(Dr. F. W. Hartman, Detroit.) Regarding Bence-Jones proteinuria, I think in the Tumor Registry of the American College of Surgeons only about 50 per cent of the cases show this reaction. It may or may not be due to the poor technique, but we have been surprised in our own cases how frequently the reaction is repeatedly negative on histologically proved cases, and also how occasionally it is demonstrated in other types of bone tumors. The microscopic sections here, particularly of the glomeruli and the glomerular capillaries, interested me because we have seen similar pictures in a group of dog kidneys where the fundus of the urinary bladder has been anastomosed to the intestine, and we get the urine excreted, and re-absorbed, and re-excreted, holding the non-protein nitrogen level at about 100 to 120 mg. We get in the urine very soon a constant albuminuria, and histological examination of these kidneys shows a very marked dilatation of the tuft capillaries; a little later they fill up with this granular protein and appear exactly the same as the pictures that Dr. Bell has shown; still later this granular material escapes — in some cases you can see the wall of the capillary ruptured, and the granular material in the capsular space. Associated with the glomerular changes we see in these animals typical nephrosis in the first 5 or 6 months and still later they go on to extensive fibrosis. I should like to ask Dr. Bell if he thinks these kidneys are typically nephrotic in the early stages, if he has had an opportunity to examine them in the stages where the glomerular changes are seen.

(Dr. Wiley D. Forbus, Durham, N. C.) We have had occasion to study just such a case as Dr. Bell has described, along with two or three other cases in which Bence-Jones protein was excreted in considerable quantity in the urine. Furthermore, we have been engaged for some time in an experimental study of the excretion of this substance through normal kidneys, and I think I can say at this time, as I have said already in a preliminary report which was published in the *Southern Medical Journal*, that our findings are identical with those of Dr. Bell, in so far as the morphological changes in the kidney tubules are concerned. In the case in which we found the most extraordinary obstructive

tubular changes we were unable to find any functional renal disturbances. We were also unable to find any lesion such as that described by Dr. Bell in the glomerulus. In view of his observation in this connection we shall go back and make another attempt to demonstrate some disturbance there. Experimentally we have done this. We have taken purified Bence-Jones' protein and introduced it into the animal's peritoneum. It is rapidly absorbed when so introduced and that absorption is followed quickly by the excretion of the substance in the urine. It is excreted by the kidneys in an unchanged form. Quantitatively about as much comes out as goes in, although it is said by some that a certain amount of the substance is destroyed. We have been unable to produce in dogs and in rabbits the obstructive tubular changes in the kidney that we have observed in the human being. However, we have succeeded in producing very definite changes in the epithelium of the proximal parts of the tubules, which we think probably are definitely related to the Bence-Jones protein. This work is still in the process of development and that is all we can say at the present time. We hope in a short time to have more data.

(Dr. Bell, closing.) There is no doubt that there are occasional cases in which uremia is due to arteriosclerosis, or to pyelonephritis. However, these are in old men who have an hypertrophied prostate and arterial disease, and I am inclined to think these are associated lesions and not due to the myeloma.

As to the incidence of Bence-Jones protein in the urine Magnus-Levy gave it as about 70 per cent and Geschickter and Copeland about 60 per cent of the cases. I think that is somewhere near the proportion that show Bence-Jones protein. The only case of renal insufficiency referable to myeloma is the blockage of the tubules by casts, aside from the exceptional case of blocking of the glomerular capillaries by protein.

SPONDYLITIS OF SWINE ASSOCIATED WITH BACTERIA OF THE BRUCELLA GROUP. William H. Feldman and (by invitation) Carl Olson, Jr., Rochester, Minn.

Abstract. Lesions of a specific spondylitis were obtained from 24 different swine and organisms of the genus *Brucella* were secured by culture procedures and by animal inoculations from 10. The affected swine were apparently symptomless and without lesions in other parts of the body. The lesions were encapsulated, abscess-like structures occupying irregular cavitations in the body of the vertebrae. Relation of the lesions of the vertebra to the usual pathology of infectious abortion of swine was not observed.

The presence in these necrotic foci of the vertebrae of Brucellae of proved pathogenicity for guinea pigs and rabbits provides a possible source of infection for farmers, packing house employees, retail butchers, and others who may handle pork in an uncooked state.

DEGENERATIVE CHANGES IN JOINTS RESULTING FROM CONTINUED TRAUMA AND INCREASING AGE, AND THEIR RELATION TO HYPERTROPHIC ARTHRITIS. Granville A. Bennett and (by invitation) Walter Bauer, Boston, Mass.

Abstract. Studies that have been in progress during the past 3 years have demonstrated quite clearly that the ability of articular cartilage to regenerate or repair in surgically created defects, or in defects due to repeated trauma, is at best very feeble and limited. These same studies have further demonstrated

that such intra-articular defects are not in themselves a cause of important joint pathology, such as the hypertrophic changes described by some workers. However, repeated trauma due to displaced patellae did result in certain animals in very marked changes similar to those observed in human hypertrophic arthritis.

Because of these findings we undertook to observe what changes might take place in human joints subjected to unusual use or repeated trauma, as well as to determine what changes resulted from wear and tear of increasing age. For the first part of this problem we studied a single joint, which had been subjected to repeated trauma or constant use, using the opposite joint as a control. In such instances one finds constant use or repeated trauma is of itself adequate cause for marked hypertrophic or degenerative changes. For the second part of the problem we collected a series of human knee joints representing various ages from the first to the ninth decades. These joints were obtained at autopsy from individuals who, so far as we could determine, had never had symptoms of joint disease. The joints were studied roentgenologically, macroscopically, and microscopically. Such studies revealed that with each succeeding decade in life beyond the second, the knee joint shows increasing pathological changes, degenerative in nature and confined for the most part to the articular surfaces. The earliest, as well as the most advanced changes observed in these joints, were identical in kind to those commonly spoken of as the characteristic lesions of degenerative or hypertrophic arthritis. From this study one is led to believe:

1. That hypertrophic or degenerative arthritis results from the wear and tear of increasing age and repeated trauma and is not the result of an inflammatory process, as some workers have contended.

2. That arteriosclerosis is not an important etiological agent in producing such lesions because either minimal or marked changes may be found in patients with marked peripheral arteriosclerosis.

3. That humans may have marked degenerative changes indistinguishable from hypertrophic arthritis without having important symptoms of joint disease.

4. That if hypertrophic or degenerative arthritis is nothing more than degenerative joint changes due to the wear and tear of increasing age, one might challenge the correctness of the use of the word arthritis in individuals with such joint changes.

Discussion

(Dr. E. T. Bell, Minneapolis.) This is a very good contribution to a subject that is of great interest at present. The lesions which Dr. Bennett showed us are quite like those of so-called arthritis deformans. Do you make a distinction between atrophic and hypertrophic arthritis, or do you think these are simply variations of the same disease?

(Dr. Bennett, closing.) We do make a distinction between Type I, atrophic, and Type II, hypertrophic arthritis. As this study would indicate, one is probably correct in believing that the joint lesions in hypertrophic arthritis are degenerative in nature and are not the result of infectious or toxic agents.

THE JOINTS IN EXPERIMENTAL SCURVY AND IN SCURVY WITH SUPERIMPOSED INFECTION. WITH A CONSIDERATION OF THE POSSIBLE RELATION OF SCURVY TO RHEUMATIC FEVER. James F. Rinehart and (by invitation) S. R. Mettier, San Francisco, Calif.

Abstract. The studies on the joints in scurvy, and in scurvy with superimposed infection here outlined represent a preliminary report on data that are as yet

incomplete. Animals used in the heart study comprise the material of this report. Joint pains, at times swelling and hemorrhage, are well known to be a part of the symptomatology of scurvy. Joint manifestations were frequently observed in the scurvy animals, both infected and non-infected, in the various series of experiments performed. It is considered significant that of the entire group of 18 animals subjected to streptococcus infection, and given the basic diet with added orange juice, in not a single instance was joint involvement observed.

Particular attention was paid to the joints in the last experiment conducted. In this experiment there were 4 animals maintained on a diet deficient only in vitamin C, in a condition of chronic scurvy without infection, 7 animals with streptococus infection maintained on an adequate dietary, and 9 animals on the same chronic scurvy dietary as the first group, but which had been infected 22 days after the onset of the experiment. Observation on the joints was made in the entire group 31 days after the onset. Of the 4 animals in the scurvy group 2 showed some stiffness and partial fixation of the knee joints. Of the 7 animals infected, but receiving an adequate vitamin C supplement to the diet, no involvement of the joints was observable. Two animals showed partial fixation of the knee on the left side due to the local cutaneous and lymph gland infection, but no joint involvement. Of the 9 animals subjected to both the chronic scurvy dietary and infection, 8 showed partial fixation of one or both knees and 3 in addition presented marked swelling of one or both knees. Five days later another animal showed mild but definite swelling of both knees. In one instance the swelling was due to a frankly suppurative arthritis, in the others not.

It is believed that these observations, although consisting of a relatively small number of animals, show a definite tendency for arthropathy in the scurvy animals and a definitely increased tendency for arthropathies in the scurvy animals subjected to a superimposed infection. In the guinea pigs on adequate dietary the infecting organism used (*Streptococcus hemolyticus* of spontaneous lymphadenitis) showed no tendency whatever to localize in or produce lesions in joints.

One or more joints were examined histologically in 30 animals as follows: acute scurvy 3, subacute or chronic scurvy 4, acute scurvy plus infection 1, chronic scurvy plus infection 8, infection followed by scurvy 4, control dietary without infection 3, and infection with adequate diet 7. The control animals and those with infection and maintained on an adequate dietary showed no pathology in the joints, synovia, or joint capsules. The animals subjected to acute scurvy presented a little fibrinous hyaline material in the joint cavity, slight or no synovial proliferation, some hemorrhage, or no change in the capsule, and a mild atrophy of the muscle. One animal showed a scattering of polymorphonuclear leukocytes in the joint space. In the group of chronic scurvy animals some hyaline material was found in the joint spaces, and a variable but usually definite proliferation of the synovia. One animal showed a little free blood in the joint space. The capsular tissues presented, as a rule, evidence of hemorrhage and some fibrous and vascular proliferation. The muscles showed edema, degeneration, reactive proliferation, and usually some hemorrhage. The animals subjected to combined scurvy and infection presented changes of a similar sort, but in general more striking with a greater amount of hyaline material in the joint space, usually more intense synovial proliferation, and greater capsular proliferation. The joint symptomatology and pathology described suggest that a condition of partial scurvy may be an important factor in the

genesis of the acute joint manifestations of rheumatic fever or the more chronic disability of the closely allied condition of rheumatoid or chronic infectious arthritis.

Although not looked for in the routine examination of animals a subcutaneous nodule, answering closely the description of the subcutaneous nodule of rheumatic fever, was found in one animal, overlying the fibula. This animal in addition showed a proliferative lesion on the mitral valve and a well defined, localized, pericardial proliferative reaction. In addition the same animal presented partial fixation and swelling of both knees. The knee joint sectioned showed a distinct synovial and periarticular proliferation.

A Consideration of the Possible Relation of Scurvy to Rheumatic Fever: The experimental data cited in which degenerative and proliferative reactions resembling those of rheumatic fever are produced in the heart valves, myocardium and pericardium by subjecting the scorbutic guinea pig to infection with streptococci, together with the data indicating an increased tendency of the scorbutic animal under the influence of infection to arthritic symptoms and pathology, naturally led to a careful analysis of other data which might support the concept that scurvy may bear a relation to rheumatic fever.

The epidemiology of rheumatic fever has long presented a challenge to the medical profession. Certain peculiarities of the disease, notably the social incidence, the age incidence, the seasonal incidence and the geographic distribution await a satisfactory explanation.

Social Incidence: It is a well recognized fact that rheumatic fever is predominantly a disease of the poor. Swift has estimated that it is 15 to 20 times more frequent in the laboring classes than in those forming the bulk of private practice. The greatest incidence occurs among the poor of elementary school age living in the cities. One need only consider the notoriously poor diet of the poorer children of metropolitan areas, such as New York and London, to realize that malnutrition and probably latent scurvy, if it exists at all, would occur under such circumstances. A number of investigators have emphasized the malnourished state of the child that is prone to develop rheumatic fever. Although relatively little attention has been directed to the clinical occurrence of latent scurvy it has recently been demonstrated clearly in Sweden by Falk, Gedda, and Göthlin to be clinically demonstrable in the spring in approximately 20 per cent of the children of elementary school age.

Age Incidence: The age of onset of acute rheumatic fever is in the vast majority of cases under 15 years — the average age of onset has been given at from 7 to 10 years. It is considered significant that it has been shown recently that children of the elementary school age (5 to 14 years) require approximately twice the vitamin C intake per kilogram for prevention of latent scurvy than adults require.

Seasonal Incidence: Suggestive evidence of a possible relation of latent scurvy and rheumatic fever is present in the concurrent seasonal incidence of the two conditions. Rheumatic fever is known to reach its peak of incidence in the spring. This is the period, of course, following a winter of diminished availability of fresh fruits and vegetables, and consequently the period of greatest incidence of scurvy and latent scurvy. Falk, Gedda and Göthlin have recently shown in Sweden that April is the period in which latent scurvy may be detected. In this connection it is of interest to note that a number of investigators have demonstrated that the milk available in winter and early spring (due to dry feed) has one half the anti-scorbutic potency of summer milk. Con-

sidering the importance of milk in the dietary of children this finding would appear of considerable significance.

Geographical Distribution: Some students of the subject have gone so far as to claim a complete absence of rheumatic fever in the tropics. All agree in its extreme rarity in this zone. Scurvy is rare in the tropics. An analysis of the dietary in the tropics would appear to give adequate reason for this. Although varying in different parts the foods eaten would appear to give an abundant supply of vitamin C.

Symptomatogical Similarities: A very suggestive parallel exists in the symptomatology of the conditions of latent scurvy and of the prerheumatic or early rheumatic state. We find general under-nutrition, fatigue, loss of appetite, loss of weight, myopathy, or pains in the limbs and chest, growing pains, irritability or nervousness, and anemia as symptoms in common. The most accurate index for recognition of latent scurvy appears to be an estimation of the capillary resistance. A diminished resistance is characteristic of latent scurvy and has been recorded in acute polyarthritis.

It is suggested that latent scurvy prepares the soil or provides the susceptible host in whom with the added insult of acute infection develop the characteristic train of symptoms and pathological evolution of acute rheumatic fever. An adequate explanation would appear to be present for the variety of organisms, notably various forms of streptococci, that have been implicated as the etiological agent.

The rather highly suggestive experimental data presented, together with the data offering an explanation for the peculiar epidemiology of rheumatic fever, would indicate a possible if not probable relation between latent scurvy and rheumatic fever. It would appear that further experimental and clinical research should be conducted to verify or refute this relation.

Discussion

(Dr. E. T. Bell, Minneapolis.) Dr. Rinehart is offering evidence that defective diets are a factor in the origin of rheumatic fever. We may of course accept this and still believe that rheumatic fever is most frequent in those exposed to cold and dampness.

SUSCEPTIBILITY TO PNEUMOCOCCUS INFECTION AS MEASURED BY SPECIES SPECIFIC AGGLUTININS. Theodore J. Curphey, New York City.

Abstract. A survey has been made of over 200 normal rabbits to determine the presence of species specific agglutinins to R pneumococci. For this purpose 5 R strains have been used in the tests. It was found that the animals tested could be divided into three groups: those having no agglutinins, those showing agglutinins in low to moderately high dilutions, and those showing agglutinins in relatively high dilutions. Following this these animals were infected intradermally with a constant dose of a smooth Type I *Pneumococcus* of high and constant virulence, and blood cultures taken at the end of 24 hours. The susceptibility of the animals was measured in terms of the bacteremic level and the extent of the local lesion at this time interval. An analysis was then made for the purpose of determining if any correlation existed between the concentration of R agglutinins and the degree of bacteremia or the extent of the local lesion. Many of the animals were treated with immune serums in comparable doses at this interval after infection, and further studies were made of the variations of

the agglutinins to the original R strains and the infecting S strain, until death or recovery took place. Following recovery the animals were tested at varying intervals for R and S agglutinins. Reinfection experiments were also carried out with observations on the variation of the R and S agglutinins. Attempts were also made to enhance natural species specific immunity by immunization with R pneumococci. These immunized animals were infected with S strains and observations made on the variation of the R and S agglutinins.

Discussion

(Dr. Francis G. Blake, New Haven.) I should like to ask the age and size of the rabbits used, because Dr. Curphey has reported a very much higher incidence of species agglutinins than we have found in rabbits weighing from 1000 to 1500 gm.

(Dr. Curphey.) The animals were chosen from the general run of stock, no attempt being made to control their age. The weights were relatively constant; they varied from 1800 to 2400 gm.

CATAPHORETIC TIME AND VELOCITY OF STREPTOCOCCI AND PNEUMOCOCCI AS ISOLATED IN STUDIES OF THE COMMON COLD, INFLUENZA, BRONCHOPNEUMONIA, AND LOBAR PNEUMONIA. Edward C. Rosenow, Rochester, Minn.

Abstract. The cultures from nasopharynges and sputum of patients suffering from colds, influenza, bronchopneumonia and lobar pneumonia, from the nasopharynx and teeth of well persons, from milk, and from inoculated animals, during and following epidemics of colds and influenza, were made on blood agar plates and in dextrose brain broth. The cataphoretic time and velocity of streptococci from dextrose brain broth cultures were determined in distilled water with the Northrop-Kunitz-Mudd apparatus, and the virulence was determined by injection into animals.

The slowing action on the respective streptococci of the serum of persons during and following attacks of the respective diseases and of well persons was studied cataphoretically.

Distribution curves of cataphoretic time and velocity of the streptococci or pneumococci isolated in these diseases were found fairly characteristic in each disease studied as these occurred in epidemic waves during the last 3 years. The cataphoretic time and velocity of streptococci isolated from the nasopharynx and teeth of well persons, of persons ill with chronic diseases, and from raw milk during epidemics of the common cold and influenza commonly resembled, sometimes markedly, that of streptococci isolated from patients suffering from colds and influenza. As epidemic waves disappeared the cataphoretic time and velocity of streptococci isolated from the nasopharynx of persons after recovery from colds and influenza, and from the nasopharynx and teeth of well persons, and from milk, became like that of streptococci isolated from the nasopharynx of well persons in non-epidemic times, and in persons ill with certain diseases it became characteristic of the disease in question.

The serums obtained from persons during convalescence from colds and influenza were found to possess specific slowing effects on the respective streptococci.

The etiological importance of streptococci in colds and influenza is emphasized.

THE ETIOLOGICAL RELATION OF FILTERABLE VIRUSES TO THE PNEUMONIAS COMPLICATING INFLUENZA, MEASLES AND WHOOPING COUGH. Howard A. McCordock, St. Louis, Mo.

Abstract. In a study of vaccine virus pneumonia in rabbits Muckenfuss and I have shown that two distinct types of reactions can be produced by different concentrations of virus. A strong virus produces a hemorrhagic and edematous consolidation with occasional irregular areas of necrosis and hemorrhage which resemble infarcts. This acute lesion has been called hemorrhagic virus pneumonia. A dilute virus induces a proliferative cellular reaction, which has been styled interstitial virus pneumonia, because the walls of the bronchi, the alveoli and the blood vessels are infiltrated with large and small mononuclear cells. Compact masses of fibrin and large mononuclear cells are seen in some of the alveoli adjacent to an involved bronchus.

The experimental hemorrhagic virus pneumonia produced in rabbits by vaccine virus is similar to the hemorrhagic and edematous lobular consolidation with foci of necrosis observed in the lungs of individuals dying a few days after the onset of symptoms of epidemic influenza. The infiltration of the interstitial pulmonary tissue in interstitial virus pneumonia in rabbits resembles the accumulation of cells seen in the interstitial bronchopneumonia that so frequently complicates influenza, measles and whooping cough in man. The complete histological picture of interstitial bronchopneumonia cannot, however, be reproduced by the action of virus alone, because the polymorphonuclear exudate in the bronchi and adjacent alveoli is usually lacking. This element can be added if bacteria are used in conjunction with dilute vaccine virus. We have used various types of bacteria, which, when injected alone, produce an ordinary lobular pneumonia.

Since interstitial bronchopneumonia can be reproduced by vaccine virus and bacteria, and because it is found in known virus diseases such as measles, dog distemper and psittacosis, we regard it as the type reaction for the combination of a virus and bacteria, but in no sense specific for a particular virus or a bacterium. A moderate cellular infiltration of the walls of the bronchi, in addition to a lobular pneumonia, is occasionally seen in bacterial infections. This combination is often found in bronchial diphtheria and has been cited as an instance of interstitial bronchopneumonia caused by a bacterium. The cases of diphtheria that we have studied show lymphocytes and plasma cells in the bronchial wall with leukocytes near the necrotic epithelial surface, but the large mononuclear cells are scarce. While we have emphasized the cellular infiltration of the bronchial wall in interstitial bronchopneumonia, it must be pointed out that this is only one element of the pathological change in this type of pneumonia. The compact fibrin masses and the large mononuclear cell exudate in the alveoli surrounding a thickened bronchus are equally characteristic, as well as the new growth of connective tissue that later appears in the infiltrated bronchial walls. While bacteria may call forth a slight cellular infiltration of the bronchial walls, there is no definite evidence that true interstitial bronchopneumonia can be produced by microöorganisms. With vaccine virus and bacteria we have been able to reproduce not only all the histological features of interstitial bronchopneumonia, but also many of the pulmonary complications that follow influenza, measles and whooping cough, such as pleurisy, empyema, lung abscess and the proliferation of the alveolar epithelium that was observed so often during the 1918–19 influenza pandemic.

If a virus is necessary for the production of interstitial bronchopneumonia, as we conclude from our experimental work, one would expect to find such an agent associated with the three human diseases that are complicated by this type of pneumonia. Of these diseases measles alone is at present generally regarded as being due to a virus. Although the etiology of epidemic influenza is unknown many investigators have suggested that it is primarily caused by a virus and we regard the similarity of the pulmonary lesions to those of measles, a known virus disease, and to experimental virus pneumonia in animals, as indirect evidence in support of such a view. Whooping cough, on the other hand, is universally regarded as a purely bacterial disease due to the Bordet-Gengou bacillus. Since interstitial bronchopneumonia is found in a high percentage of fatal cases of whooping cough it was necessary to seek evidence of the presence of a virus in this disease, if our conclusion that a virus is necessary for the production of this type of pneumonia was to stand.

Last year I reported the finding of intranuclear inclusions in the lungs of 12 out of 35 children who had died of pertussis and their absence in all but 2 children of a control series of 90 autopsies. Since then 18 out of 40 cases of pertussis (45 per cent) have shown these inclusions. The presence of cellular inclusions in such a high percentage of our cases of whooping cough is strong evidence of the possible association of a virus with this disease. In this connection it is interesting to recall the history of three other diseases, namely, hog cholera, canine distemper, and psittacosis, which for years were regarded as being due to specific bacteria but now are known to be caused by viruses.

The similarity of virus pneumonia in animals to the pneumonias complicating influenza, measles and whooping cough, suggests that viruses are associated with these three diseases, and the presence of intranuclear inclusions in whooping cough strengthens the evidence for the presence of a virus in this disease.

Discussion

(Dr. Francis G. Blake, New Haven.) The theory is obviously a very interesting one. I should like to ask what the character of the cellular reaction is in the interstitial infiltration: whether it is constantly a mononuclear cell infiltration, as I judge it is from the slides, or whether there is any polymorphonuclear interstitial infiltration; also whether you consider the mononuclear character of the cellular interstitial infiltration to be the important point. I raise that question because grossly quite similar pictures of interstitial infiltration without polymorphonuclear exudate in the alveoli or bronchioles can be found in animals injected with bacteria in which no virus has been introduced.

(Dr. McCordock, closing.) Of course the important cellular element in interstitial bronchopneumonia is the mononuclear cell infiltration, which consists of large mononuclear phagocytes, lymphocytes, and occasionally plasma cells. In animals injected with vaccine virus, when strong virus is used, one often sees an interstitial cellular infiltration consisting almost exclusively of polymorphonuclear leukocytes, as one might expect following the destruction of pulmonary tissue. In general, the large mononuclear cell infiltration is characteristically associated with viruses, as was pointed out by Ledingham in a study in which vaccine virus was introduced into the skin, and we believe that vaccine virus calls forth a mononuclear cell infiltration. In addition to this mononulcear cell infiltration, vaccine virus can produce not only the acute lesions seen in influenza, but also the more chronic ones, and by the addition of bacteria to the

virus one may reproduce many of the pulmonary complications of influenza, whooping cough and measles. That is far more than can be done with bacteria of any type, or with any other irritating substance. Winternitz has shown that irritating gases will produce a lesion not unlike the hemorrhagic virus pneumonia we have described, and others have shown that fluid cultures of *B. influenzae* will produce similar lesions, but with neither of these substances has any one ever been able to reproduce the chronic type of interstitial pneumonia, or the pulmonary complications seen following influenza, whooping cough or measles.

FRIEDLÄNDER BACILLUS PNEUMONIA. Charles T. Olcott, New York, N. Y.

Abstract. The clinical and autopsy findings of 5 acute cases of pneumonia proved by blood culture to be due to Friedländer's pneumobacillus are presented. Four of them showed a lobar, the fifth a lobular distribution. All were in males between 38 and 55 years of age, and large fatty livers were found in 3. In 4 cases the white blood count was less than 7000, in 1 less than 2000. In 3 the pulmonary alveoli contained large mononuclear phagocytic cells in greater numbers than polymorphonuclears.

As all the cases were of short duration (2 days to about a week), it is postulated that a primary mononuclear reaction is characteristic of at least some Friedländer pneumonias.

Discussion

(Dr. Francis G. Blake, New Haven.) Among other things it seems to me that this report illustrates the caution one needs to preserve in attempting to relate mononuclear or polymorphonuclear cell infiltration to virus or bacterial infection.

(Dr. Nathan Chandler Foot, New York City.) I think the importance of these monocytes or mononuclear cells in these exudates in the lung is very often overlooked, on account of the subjectivity of the observer. In Germany they have been explained away largely on the basis that they represent desquamation, and for that reason they have been neglected. These are much more common in pneumonic exudates than is generally believed; most people observe them and pass over them, and I think Dr. Olcott's objectivity is to be commended.

(Dr. E. T. Bell, Minneapolis.) Dr. Foot, how do you classify the alveolar cells in tuberculous pneumonia?

(Dr. Foot.) I think they belong in the same category. There is desquamation, but the number of cells desquamated is rather small, as compared to the number of cells migrating into the alveoli.

(Dr. Howard T. Karsner, Cleveland.) There are three questions I should like to ask. (1) Is a low leukocyte count in the blood a phenomenon frequently noted in the reported cases of Friedländer bacillus pneumonia? (2) Were the patients in the hospital for a sufficient length of time so that repeated blood counts could be made to determine whether the leukocyte counts Dr. Olcott reported were continuous or terminal depressions? (3) Did the bone marrow show cytological changes or bacterial invasion?

(Dr. Olcott, closing.) From a survey of the literature I have found three references which quote a leukopenia (Lord, Belk and Fremel *et al*).

With relation to the time in the hospital, the man with the lowest count was

in the hospital only 9 hours, and only one case was in over 2 days. We unfortunately had no repeated blood counts.

With regard to the bone marrow, I have studied only 1 case and in this there was no characteristic departure from normal.

THE GENESIS OF ONE GROUP OF SECONDARY PNEUMONIAS. Virgil H. Moon, Philadelphia, Pa.

Abstract. Pulmonary congestion and edema, not caused by cardiac deficiency, precede the development of a group of secondary pneumonias. Circulatory failure of the shock type produces marked pulmonary congestion and edema resulting from atony of capillaries and venules. Krogh showed that capillary atony and dilatation result from all types of capillary poisons. Severe toxemia of diverse origin causes such vascular atony and permeability to develop gradually. Severe burns, extensive surgical procedures, toxemias of pregnancy, pancreatitis, intestinal obstruction, mesenteric thrombosis, severe jaundice or infections of high virulence may cause circulatory deficiency of this type.

Secondary pneumonia following burns is typical of this group. The lungs are deep red, heavy, edematous, and consolidated in irregularly distributed patches. Fibrin is deficient and the consolidation is less dense than in primary pneumonias. The results of bacteriological studies are not uniform. Frequently mixed cultures result, including combinations of pneumococci, streptococci, staphylococci and *Micrococcus catarrhalis*. Pneumonia following influenza is of this type and is indistinguishable from that following burns or other toxemias.

Toxemias of diverse origin may produce circulatory deficiency resulting in pulmonary congestion and edema. One group of secondary pneumonias results from infection of such lungs with the various pathogenic organisms present in the respiratory tract.

Discussion

(Dr. E. T. Bell, Minneapolis.) It was pointed out by some one in a paper presented at the last annual meeting that cultures from the lungs of practically all postmortem cases are positive. I should like to ask Dr. Moon if that is his experience, and if he thinks we can form any conclusions from the postmortem cultures of the lung. I should also like to ask if he thinks that areas of atelectasis play any part in these secondary foci in pneumonias of this type.

(Dr. Moon, closing.) It is perfectly true that cultures from lungs at postmortem almost always contain organisms. The same uncertainty exists in cultures from Friedländer's pneumonia and from pneumonia following any of the other known infectious agents. Neither is there any characteristic type of organism that predominates in influenzal pneumonia, and I wish to emphasize the analogy between influenzal pneumonia and the pneumonias under discussion. I believe that they belong in this group. This belief is strengthened by the fact that Underhill and Ringer reported an increased concentration in the blood in those cases that ran a rapidly fulminating course. The hemoglobin in such cases ranged from 110 to 140. They found that patients who recovered from influenza had no increased blood concentration.

I have made no observations on the relation of atelectasis to the type of pneumonia that I have presented.

PNEUMONIA IN NEWBORN INFANTS. Margaret Warwick, Buffalo, N. Y.

Abstract. In a series of 240 autopsies upon newborn infants dying during the first 10 days of life pneumonia was found in 46, or 19 per cent. Three of these were discarded because their etiology was evident and they showed a different type from the others. That left 43, or 17 per cent of cases of pneumonia in newborn infants for study and analysis.

Of these 10 were stillborn, 8 lived less than 12 hours, and 6 less than 2 days, making 24, or 56 per cent, which must have developed their pneumonia while yet *in utero*. Two of these were of but 5 months gestation. Twenty, or 46.5 per cent, had no other pathological lesions and, without pathological examination, would have been passed as atelectasis. Twenty-one, or 50 per cent, showed traumatic lesions from difficult births and 2, or 4.8 per cent, showed congenital anomalies.

Only 11, or 25.6 per cent, were born by spontaneous deliveries with an average labor of 13 hours, while the others had interference of some kind. The infants varied in size from 450 to 4225 gm. with an average of 2871 gm. Their positions *in utero* showed a large percentage of abnormal ones. These various abnormalities suggest that there might have been cause for asphyxia, which would stimulate premature respirations that would draw amniotic fluid, which might or might not be infected with pathogenic organisms, into the alveoli of the lungs.

Amniotic fluid, in variable amounts, is a frequent finding in the lungs of newborn infants. This is recognized by the presence of fat, cornified epithelium from the surface of the body, lanugo, fluid and masses of bile salts from the meconium, which are present in various ratios. This foreign material is usually in the midst of an area showing exudation of polymorphonuclear leukocytes. In this series the various constituents of amniotic fluid were found in 175, or 73 per cent of the total series of 240. And in the 43 cases of pneumonia it was present in 37, or 86 per cent.

Gram stains of the lungs showed bacteria present in 11, or 25.5 per cent. The general opinion is that these pneumonias are caused by the aspiration of amniotic fluid which has become infected by pathogenic organisms from premature rupture of the membranes. In this series only 5, or 12 per cent, had rupture of the membranes long enough for such a thing to take place. In 27, or 63 per cent, the membranes had ruptured less than 1 day before birth. In 11, or 25.8 per cent, the time was not recorded. In the 3 cases where Cesarean section was done the membranes were intact until the child was delivered. Therefore, infections of the amniotic fluid could not have taken place unless the bacteria could have passed through the intact membrane or in tiny, unsuspected tears, which is highly improbable.

Atelectasis is a frequent accompaniment of pneumonia in the newborn and is usually recognized, while the pneumonia is not. In this series there were large areas of atelectasis in 20, or 46.5 per cent, small areas in 12, or 28 per cent, and none in 11, or 25.6 per cent. The exudate and foreign material were usually found in the center of the atelectatic areas.

Former observers have thought that bacteria were the cause of pneumonia in the newborn, but this series points toward aspirated amniotic fluid as the etiological factor. It is also possible that either may cause similar lesions. Chemical or mechanical irritation may cause acute inflammation and exudation in other parts of the body. Pneumonia occurs in cases where there is no demon-

strable chance of bacteria entering into the amniotic sac, and it is usually associated with large amounts of amniotic fluid in the lung alveoli. And, whatever the cause, pneumonia in the stillborn and those dying during the first few days of life is a definite pathological entity and should receive more recognition from both obstetricians and pediatricians. It may cause death directly by the exudation or indirectly by preventing proper aeration of the lungs.

Discussion

(Dr. Sidney Farber, Boston.) I think that we ought to differentiate sharply between the reaction in the lungs following aspiration of amniotic fluid which contains vernix caseosa, cornified cells, and so on (the so-called normal amniotic sac contents), and that following aspiration of amniotic fluid that contains meconium. I think we are dealing with two different things. Some years ago we studied the lungs of rabbits following insufflation of amniotic fluid that contained vernix and cornified cells. That study combined with observations on lungs of newborn infants led us to conclude that the amniotic sac contents alone aroused no important reaction in the lungs, or at best a very slow mononuclear reaction. We found no evidence of a toxic or poisonous action of amniotic fluid. However, aspiration of amniotic sac contents, to which meconium has been added, gives an entirely different picture.

(Dr. E. T. Bell, Minneapolis.) It is remarkable how often one finds meconium in the alveoli in newborn infants. We had one case with a well developed purulent pneumonia in an infant who lived only 8 hours. There is no question that some of these cases are intra-uterine in origin.

(Dr. Edward C. Rosenow, Rochester, Minn.) I should like to ask if the matter of seasonal incidence has been considered. During experiments with streptococci of high virulence from cases of influenza it is not uncommon to find that organisms injected even intratracheally in pregnant animals will appear in the lungs of the fetuses. In view of the fact that normal persons become carriers of the streptococcus resembling in cataphoretic time and velocity and virulence the streptococcus of influenza in winter, it seems to me it would be interesting to determine whether or not there was a seasonal occurrence of pneumonia in newborn infants.

(Dr. Warwick, closing.) I agree that the question of amniotic fluid without meconium is of importance. It is hard to believe that just ordinary fluid causes pneumonia, but I find the great majority of my cases show meconium. That is why I took one series to show just meconium and the cornified epithelial cells.

In answer to Dr. Rosenow's question about seasonal incidence I do not know about that. I do know that these tended to occur in groups. Perhaps they had a seasonal incidence. I will look that up when I get back to Buffalo.

I did not have time to mention that two of the cases were in infants of only 5 months gestation, in which the alveoli were imperfectly formed, and the primitive alveoli were filled with polymorphonuclear leukocytes. In this case I was not able to demonstrate meconium with certainty, but there were granules there that looked like meconium, and I showed it to other pathologists who thought it might be meconium in which the bile salts did not have the color they would have later. I think practically all my cases showed meconium, but it varied in amount. I think perhaps a small amount of meconium might not cause a pneumonia, whereas a large amount would. Then, too, the condition of the infant might have something to do with it. If we had an infant who was subjected to

unusual procedures during birth or before, it might be more susceptible to the action of the amniotic fluid containing irritating material.

STUDIES IN PNEUMONIA OF INFANCY AND CHILDHOOD BY THE WHOLE LUNG SECTION METHOD. Irving Graef and (by invitation) Charles Hendee Smith and Elizabeth Torrey Andrews, New York, N. Y.

Abstract. Clearness in the pathological diagnosis of pneumonia of infancy suffers from a limitation of anatomical studies to small blocks of tissue. MacNeil and his coworkers studied whole lung paraffin sections, but did not separate the common varieties of pneumonia beyond bronchopneumonia and alveolar (lobar) pneumonia.

At Dr. Smith's suggestion we have sectioned whole lung blocks in paraffin thin enough (8 to 12 microns) to combine topographical and histological studies. We have studied the lungs of 96 infants, aged 1 week to 4½ years, by this method.

Eighteen showed no evidence of pneumonia. Four showed rare forms of pneumonia. The remaining 74 cases were classified anatomically as follows:

Lobar Pneumonia: Although frequently found during life in infancy and childhood, it is a rare lesion at autopsy on account of the low death rate. Five cases, 15 per cent of those sectioned, corresponded to the picture of lobar pneumonia as seen in adults, and showed diffuse hemorrhagic or fibrinopurulent alveolar exudate. Lymphangitis and septal involvement were found in all, pleurisy in 4 of the 5 cases, hemorrhages and abscesses in 3.

Lobular Pneumonia: We studied 16 cases showing as the characteristic lesion hemorrhagic or fibrinopurulent exudate in the alveoli of the lobule. Bronchiolar involvement is usually limited to those in affected lobules, where they show acute suppuration. There is irregularity in the distribution of lobular involvement and in the density of the exudate. This form is often confluent and tends to involve especially the lobules about the hilum. In 3 cases a whole lobe was involved, yielding a gross appearance of lobar pneumonia. Peripheral lobules are less often affected. Foreign material is regularly found within the bronchi. Pleuritis and lymphangitis are rare. Parenchymal and bronchiolar abscesses and hemorrhage are common.

Fifty-three cases show evidence of *bronchopneumonia*, which could be readily divided into two anatomical varieties. One of these is characterized by infiltration of the outer layers of the walls of the bronchi and bronchioles with mononuclear cells (histiocytes or fibroblasts and lymphocytes) and suppurative endobronchiolitis. Parenchymal involvement is limited to a few of the alveoli immediately adjacent to the bronchi, the exudate consisting of a few mononuclear cells and a little fibrin. This lesion may be discrete or confluent. The confluent form shows coalescence of more massive lesions, resulting in a picture resembling confluent sublobular or lobular consolidation due to collapse of the intervening intact parenchyma.

For the second variety we have used the term *broncholobular pneumonia*. There is characteristic mononuclear infiltration of the bronchial wall, extensive suppurative endobronchiolitis, and in addition a fibrinous or fibrinopurulent alveolar exudate involving whole lobules, in some cases a major part of the lobe.

The unmixed form comprised 21 cases, the mixed 32 cases, 1 of which showed only doubtful evidence of true lobular involvement. Both forms are disseminated; unilateral involvement was encountered only once. Varying degrees of bronchial involvement are common when various lobes are compared and in the

same lobe. Collapse occurred in all but 2 cases, both belonging in the unmixed group. It was so extensive in 2 cases as to simulate lobar consolidation.

Lymphangitis of the septa, pleuritis, abscess formation and hemorrhage are rare in pure bronchopneumonia, and frequent in broncholobular pneumonia. Evidence of aspiration of foreign material is infrequent in both forms. Thrombosis was rarely encountered.

This analysis suggests certain simple mechanisms that may determine the type of lesion found. Abscesses and ruptured bronchioles occur far more frequently in broncholobular pneumonia than in the pure bronchial form, suggesting that involvement of the lobule occurs by secondary extension from the affected bronchiole. Another mechanism may be endobronchiolar extension of the exudate or infectious agent to the collapsed lobule. Occasionally there is primary diffuse involvement of the wall of the bronchus, the septa, and the terminal lobules. Broncholobular pneumonia appears to be a more severe or advanced stage than uncomplicated bronchopneumonia.

In lobular pneumonia aspiration appears to be the primary mode of involvement, occurring most frequently in feeble infants (all 16 cases were in newly born, debilitated, or congenitally defective infants; 11 of the 16 were under 6 weeks of age). Two mechanisms may account for the lesions. There may be infection of the lobules by aspirated infective material or local infection of an obstructed bronchiole with extension through or rupture of its walls and extension to the alveoli of the lobule.

Permanent hilum involvement in aspiration lobular forms and in the broncholobular forms may be related to shallow breathing with minimal ventilation in this portion of the lung, especially in debilitated infants, thus promoting stasis.

Discussion

(Dr. George R. Callender, San Antonio.) I should like to ask whether any bacteriological studies were made in relation to the type of pneumonia.

(Dr. Francis G. Blake, New Haven.) Did any of these cases follow measles or other infections?

(Dr. Rufus Cole, New York City.) May I ask the age of the children who had the lobar type of pneumonia?

(Dr. Howard T. Karsner, Cleveland.) In continuation of Dr. Cole's question I should like to have Dr. Graef explain the criteria for the anatomical diagnosis of lobar pneumonia.

(Dr. E. T. Bell, Minneapolis.) This is an important demonstration in the study of the problem of pneumonia by the whole section method. As I understand it, these are sections of lantern slide size which are projected directly. This method should be of value in teaching.

(Dr. Blake.) While no one will deny that for practical clinical purposes it may be desirable to retain the term lobar pneumonia, as representing a fairly characteristic clinical picture, I think one hesitates to try and draw any sharp distinction between lobular pneumonia and lobar pneumonia, because of the fact that the picture of pneumococcal pneumonia as a whole, as I have tried to indicate in some of our experiments, runs the whole gamut from focal lobular pneumonia to a diffuse lobar pneumonia. Furthermore, in a great many cases coming to autopsy one frequently finds lobar consolidation in one lobe and lobular consolidation in another lobe in cases in which there was apparently only one organism concerned in the infection — the pneumococcus. While the dis-

tinction has certain practical uses, it seems to me there is a certain danger in too sharp a differentiation which tends toward a departmentalization of our conceptions of infection with the pneumococcus. The reason why one wishes to know the age of the children who had a diffuse lobar consolidation is because of the theory, without supporting experimental evidence, that increased sensitiveness or allergy is responsible for a diffuse lobar consolidation, as contrasted with a focal lobular consolidation. I would call attention to the fact that the results of our studies in guinea pigs are quite inconsistent with the notion that a high degree of reactivity is related to a diffuse, rapidly spreading lobar pneumonia, because of the fact that our less sensitive animals presented a dermal lesion more nearly resembling a lobar pneumonia than our more sensitive animals, which presented a lesion more nearly resembling lobular pneumonia.

(Dr. Graef, closing.) In reply to Dr. Callender's question, bacteriological studies have been made in a large number of these cases, in life both by throat swabs and blood cultures, and also by postmortem cultures of the lesions in the lung, but we have as yet made no attempt to correlate these.

In answer to Dr. Blake's question with reference to measles, one case of bronchopneumonia followed measles.

In answer to Dr. Cole the age distribution of the lobar pneumonias was one infant 1 month old, and the others distributed unevenly through the first year.

In reply to Dr. Karsner's question about the criteria for the anatomical diagnosis of lobar pneumonia, this covers the entire question as to whether or not the term lobar is merely a quantitative expression of involvement of the lung. We have separated aspiration forms from primary infective lobular pneumonia. One of the distinguishing features of the aspiration forms is the regular demonstration of foreign material in the affected lung. Furthermore, it is encountered in a special group of infants, *i. e.*, the newly born, the debilitated, or the congenitally defective.

In primary infectious forms the lesion may be lobular, or it may occupy the major part of the lobe, primarily or by confluence. Occasionally, as in the cases shown on the screen, the difference in the nature of the exudate from field to field microscopically, from lobule to lobule, is much less marked than in advanced lobar pneumonia, as one usually sees it in adults.

In the particular child shown with lobar pneumonia the exudate within 48 hours after an abrupt onset of the disease was essentially an edema fluid in which microörganisms, red blood cells and leukocytes were seen in almost every field. Naturally I had to limit my demonstrated material to the method we used, but gross pictures have been compared in all cases with essential microscopic findings.

If I might go back to the discussion of Dr. Warwick's paper we are very anxious to separate the aspiration lobular pneumonia from primary infective lobular pneumonia which follows infectious diseases. Children who are unable to cough will very readily aspirate food material and vomitus, and they show the picture of lobular consolidation with prominent hilum involvement. Lobular involvement may be confluent occasionally to the extent of a lobe. Where there is definite evidence of aspirated material in the lungs, whether it is meconium, bile pigment or epidermal cells and amniotic fluid, unless there is the characteristic mononuclear cell infiltration in the outer layers of the walls of the bronchioles we feel the term lobular or sublobular pneumonia would be a safer description of the lesion than bronchopneumonia. It is true that the bronchial walls

are affected in aspiration pneumonia, but only in the affected lobule, which I think is quite different from the disseminated lesion of the bronchi following a respiratory infection.

ATELECTASIS OF THE NEWBORN. Sidney Farber and (by invitation) James L. Wilson, Boston, Mass.

Abstract. The following conclusions are based on experimental work and a pathological and clinical study of the lungs of several hundred full term and premature newborn infants. The lungs do not expand fully with the first breath. A few days are required before complete expansion is reached in the full term infant, and a period of 6 weeks or longer in the premature infant. Areas of previously unexpanded lung (initial atelectasis) can be differentiated from collapsed lung tissue which has once been expanded (resorption atelectasis) by observations on the size, shape, and position of the alveolar lining cells. The lungs of early premature infants differ from those of full term infants by the presence of areas of unexpandable lung tissue characterized by scattered masses of cells, identical in appearance with cells lining fully formed alveoli. No lumens are present. These are similar to masses of cells without alveolar formation in the lungs of a 3½ months fetus.

Since atelectasis may be present normally in the full term infant for several days it should not be accepted as a complete and satisfactory cause of death in the first few days of life. We have shown by measurement of the resistance to expansion of the lungs of dead infants, and dead and living animals, that the cohesion of the moist surfaces of the respiratory passages in collapsed lungs offers a considerable resistance to the entrance of air and that a relatively great force is required to overcome this cohesion and to separate the air passages during the initial expansion of an atelectatic lung. The very first breath of every newborn infant may thus be its most difficult one, and therefore, for a variable period after birth, especially vigorous inspirations must be maintained until atelectasis finally disappears. This factor is always present in the newborn infant. It may be combined with any of the following conditions, in explanation of the pathogenesis of atelectasis of the newborn:

1. An imperfectly developed or an injured respiratory center (hemorrhage).
2. An imperfectly developed thoracic mechanism (premature infants) when the contraction of the intercostal muscles and the bony resistance of the thorax do not furnish an effective *vis a tergo* for the efficient action of the diaphragm.
3. Bronchial obstruction due to aspiration of amniotic sac contents, mucus or blood.

Discussion

(Dr. Rafael Dominguez, Cleveland.) I should like to call the attention of Dr. Farber to the fact that the initial response to deformation in organic elastic bodies is well known. It has been known since the experiments of Weber, from Göttingen, on the elastic properties of silk threads, which require a preliminary preparation before the elasticity can be quantitatively studied. This property has been found in many colloidal substances. It is familiar in the case of chewing gum, and it forms an important development in the physical literature, under the name of thixotropy.

THE SHWARTZMAN PHENOMENON IN THE LUNGS OF RABBITS. John Cohen (by invitation), New York City.

Abstract. In a study of the pathogenicity of the organisms of human lung abscess there is encountered a group of non-chromogenic, strictly anerobic, gas-producing Gram-negative bacilli with foul odor which elicit a severe gangrenous bronchopneumonia and empyema in the lungs of rabbits when injected intratracheally. This ability is only shared by these organisms, for the other organisms of lung abscess do not produce these lesions (*i. e.*, cultures of streptococci, diphtheroids, *B. ramosus*, *B. fusiformis* and other aerobic organisms, singly or in combination). Rabbits dying spontaneously in the laboratory and examined routinely show a hemorrhagic lobar pneumonia which differs entirely from the gangrenous type produced.

We then attenuated the virulence of these organisms in different culture media so that mild lesions (patchy hemorrhagic bronchopneumonia without necrosis) were produced in the lungs of rabbits or none at all. If an organism of such diminished virulence was injected intratracheally and a mild reaction induced in the lungs of rabbits, and then in 24 hours the homologous culture filtrate was injected intravenously, the lesions in the lungs appeared at a maximum, namely, gangrenous bronchopneumonia and empyema, thus eliciting the Shwartzman phenomenon in the lungs. This phenomenon has been previously demonstrated by the use of sterile filtrates in the kidney and liver (Shwartzman), in the stomach (Karsner, Ecker and Jackson), in the knee joints (Moritz and Morley), and in the intestinal tract (Gratia and Linz).

Discussion

(Dr. Howard T. Karsner, Cleveland.) The discovery of the Shwartzman phenomenon is an extremely important contribution. In its simplest terms it appears to be essentially due to vascular injury. In Dr. Cohen's communication it is apparent that the primary dose of filtrate had to be adjusted delicately so that the injury was comparatively slight. The later injection augmented the vascular injury, as indicated by the hemorrhage and thrombosis. Is there a specific relation between the human pulmonary disease, from which Dr. Cohen isolated the organisms, and that produced in the lungs of the experimental animals? In other words, is it not possible that filtrates of other organisms used in similar fashion produce essentially the same lesion?

(Dr. Francis G. Blake, New Haven.) I think one has to take exception to the statement that other organisms have not satisfactorily produced lung abscesses in experimental animals. Certainly there is no difficulty in experimentally producing typical necrosis and lung abscess in monkeys with pure cultures of hemolytic streptococci.

(Dr. Cohen, closing.) In answer to Dr. Karsner, by injecting the toxin or the toxic filtrate intratracheally into rabbits, and then injecting the toxic filtrate intravenously, no lesions in the lungs are obtained. It appears that unless a mild lesion in the lung is produced with a live and attenuated organism the phenomenon cannot be obtained after the intravenous injection. We have not studied any other organism, because for the present we have paid undivided attention to the non-chromogenic, strictly anerobic, Gram-negative bacillus, which has proved uniformly pathogenic.

In reply to Dr. Blake, we have not found at any time that injection of the anaerobic streptococcus into the lungs of rabbits produced any lesion. The *Streptococcus putridus* (Schottmüller), which produces hemolysis on blood plates and gas, and foul odor on suitable media, will also produce a hemorrhagic pneumonia, but not of the type of gangrene associated with this Gram-negative anerobic bacillus.

IMMEDIATE PNEUMOCOCCUS TYPING DIRECTLY FROM SPUTUM BY THE NEUFELD REACTION. Albert B. Sabin (by invitation), New York City.

Abstract. Neufeld observed that when pneumococci are mixed with specific immune serum there occurs in addition to agglutination a *Quellung* (swelling) of the peripheral zone of the organisms. Early attempts to apply this observation to the typing of pneumococci in sputum were not uniformly successful for various reasons. A study of the various factors involved revealed the following to be of great importance: (1) The horse antipneumococcus serums commonly used for typing were unsuitable for this method because they frequently gave non-specific reactions, which could not be satisfactorily eliminated by dilution; (2) carefully prepared rabbit serum gives absolutely specific results; (3) the preparation must be observed in the moist state, and alkaline methylene blue aids in visualization.

The following method was successfully employed with sputum from 100 cases of lobar pneumonia. To a small fleck of sputum a small loopful of rabbit serum and a loopful of alkaline methylene blue are added. This preparation (hanging drop) is immediately observed with the oil immersion lens. When the organism is of the same type as the serum a characteristic zone of ground glass appearance is seen around it. This method was successful in every case; it dispenses with the use of mice and permits a correct determination of pneumococcus type directly from the sputum within a few minutes.

Discussion

(Dr. Roderick Heffron, by invitation, Boston.) I should like to say a word about this method of typing. At the State Bacteriological Laboratory in Boston we have been using the Neufeld method of typing along with the Krumwiede, Sabin and tube agglutination methods for about 6 months. During the past 4 months the Neufeld method has been used routinely.

For this method of typing we have used the technique kindly demonstrated to us by Dr. Kenneth Goodner. Recently we have altered this to the extent of using flat slide preparations instead of the original hanging drop method.

Pneumococcus typing of any sort is preferably carried out on fresh material; however, the majority of our specimens come by mail and are, on the average, from 12 to 24 hours old when received. Despite the age of such specimens we have had extremely gratifying typing results using the Neufeld technique.

During the past 6 months sputums from 109 cases of pneumonia of various sorts have been typed by this method. Forty of these were correctly diagnosed as Types I, II, or III. The results in two others were questionable; later these were found to be of the type first suspected.

Of the 109 cases typed by this method results (for Types I, II, or III) were negative in only 3, which later proved to be one of these types. In each of these instances no pneumococci were seen in the original preparations, but they were

isolated following mouse inoculation. So far it has been possible to check the results of every Neufeld typing by at least one other method.

In Massachusetts, as elsewhere, time is a most important factor in the successful serum treatment of lobar pneumonia. During the brief period the Neufeld technique has been used we have been able to save as much as 12 to 24 hours on our reports in many instances.

The method has also proved valuable for typing broth cultures, cultures on solid media, and mouse exudates where the flora is mixed and pneumococci are few. In the latter case the Neufeld technique has yielded positive results when other methods were not applicable.

If, after further study, we continue to find the Neufeld method as reliable as it now appears, the procedure will be taught to our collaborating technicians throughout the state. Rabbit typing serum will be supplied to them in order that the method may be routinely used.

(Dr. Frank B. Lynch, Philadelphia.) It seems to me from the appearance of these slides that there might be some confusion in the appearance of these organisms with that of the Type III pneumococcus. I should like to ask if there has been any difficulty in that respect.

(Dr. Sabin, closing.) In response to Dr. Lynch, I can say that among the 100 cases there were 4 of Type III, and in no instance, in the hanging drop preparation, did the Type III organism show a capsule.

READ BY TITLE

Characteristics of Tuberculous Ulcers in Skin of Syphilitic and Non-syphilitic Rabbits. Joseph D. Aronson and (by invitation) David R. Meranze, Philadelphia, Pa.

The Types of Hyperthyroidism; their Relation to the Previous Condition of the Thyroid Gland. Leon K. Baldauf and (by invitation) Arthur Purdy Stout, New York, N. Y.

A Biometrical Study of the Size of Liver and Spleen in Different Diseases for Differential Diagnosis. Moses Barron, Philadelphia, Pa.

Generalized Skeletal Demineralization Associated with a Cervico-Thoracic Intramedullary Tumor. Hugo A. Freund, Detroit, Mich.

Production of Tuberculin Type of Hypersensitiveness with Ordinary Protein Antigens. John A. Hanks (by invitation), Washington, D. C.

Changes in the Lower Extremity Bones in Association with Arteriovascular Disease. Henry L. Jaffe and (by invitation) Maurice M. Pomeranz, New York City.

Thrombosis and Pulmonary Embolism. James S. McCartney, Minneapolis, Minn.

The Morphology of Prostatic Corpora Amylacea. Robert A. Moore, Cleveland, O.

Bacterial Variations in the Colon-Aerogenes Group. Leland W. Parr (by invitation), Washington, D. C.

REPORT OF A CASE OF SITUS INVERSUS VISCERUM. H. C. Schmeisser and (by invitation) T. C. Moss, Memphis, Tenn.

A STUDY OF THE EFFECT OF RADIUM RAYS ON CERTAIN BACTERIA. Roscoe R. Spencer and Herman A. Fisher (by invitation), Washington, D. C.

GONOCOCCIC MENINGITIS. Max M. Strumia and (by invitation) Jacob J. Kohlhas, Bryn Mawr, Pa.

THE INFLUENCE OF THE CALCIUM INTAKE ON THE THYROID GLAND OF THE ALBINO RAT. Juanita Thompson, Toronto, Canada.

THE BACTERIOLOGY OF HUMAN ACTINOBACILLOSIS. Luther Thompson (by invitation) and D. C. Beaver, Rochester, Minn.

SOME EXPERIMENTS ON CYSTINURIA. Vincent DuVigneaud and Hubert S. Loring (by invitation), Washington, D. C.

FURTHER STUDIES ON THE COAGULO-FLOCCULATION TEST FOR MALIGNANT TUMORS. Emil Weiss, Chicago, Ill.

THE RELATION BETWEEN THE PATHOLOGICAL AND RADIOLOGICAL FINDINGS IN TUMORS OF THE LUNG. Isaac Levin, New York, N. Y.

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